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Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings: a safety and feasibility study

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5 2 Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings:
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2
3 50 **ABSTRACT**

4
5 51 **OBJECTIVE**

6
7 52 To assess the safety and feasibility of small volume plasma exchange (SVPE) as an alternative to
8
9 53 standard plasma exchange (PE) or intravenous immunoglobulin (IVIg) for Guillain-Barré
10
11 54 syndrome (GBS) patients.

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13
14 55 **DESIGN**

15
16 56 Non-randomized, single arm, interventional trial.

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18 57 **SETTING**

19
20 58 National Institute of Neurosciences and Hospital, Dhaka, Bangladesh.

21
22 59 **PARTICIPANTS**

23
24 60 Twenty adult (>18 years) patients with GBS presented within 2 weeks of onset of weakness who
25
26 61 were unable to walk unaided for more than 10 meters.

27
28 62 **INTERVENTIONS**

29
30 63 SVPE involves blood cell sedimentation in a blood bag and removal of supernatant plasma after
31
32 64 blood cells are re-transfused. This procedure was repeated three to six times a day, for eight
33
34 65 consecutive days.

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36 66 **OUTCOME MEASURES**

37
38 67 Serious adverse events (SAE) were defined as severe sepsis and deep venous thrombosis related
39
40 68 to the central vein catheter (CVC) used during SVPE. SVPE was considered safe if less than 5/20
41
42 69 patients experienced a SAE, and feasible if 8 L plasma could be removed within 8 days in at least
43
44 70 15/20 patients.

45
46 71 **RESULTS**

47
48 72 Median patient age 33 years (IQR 23-46; range 18-55); 13 (65%) were male. Median MRC sum
49
50 73 score was 20 (IQR 0-29; range 0-36); three (15%) patients required mechanical ventilation. One
51
52 74 patient developed SAE (severe sepsis, possibly related to CVC). Minor adverse effects were

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3 75 transient hypotension in 10 (50%) patients; CVC-associated bleeding in 10 (50%); transfusion
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5 76 reaction to fresh frozen plasma in 4 (20%); and hypo-albuminemia, anaemia or electrolyte
6
7 77 imbalance in 4 (20%). Removal of 8 L plasma was possible in 15 (75%) patients. GBS disability
8
9 78 score improved by at least one grade in 14 (70%) patients four weeks after SVPE started. No
10
11 79 patients died.

13 80 CONCLUSION

16 81 SVPE seems a safe and feasible alternative treatment to standard PE or IVIg for GBS; further
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18 82 studies of clinical efficacy in low-resource developing countries are warranted.

20 83

22 84 TRIAL REGISTRATION

24 85 Clinicaltrials.gov NCT02780570 on May 23, 2016

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3 94 **Strength and limitations of the study:**
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7 96 1. The strength of this study underlies the novel and simple technique of SVPE, which is
8
9 97 much less expensive than conventional immunotherapies (plasma exchange and
10
11 98 intravenous immunoglobulin)

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13 99 2. SVPE is corroborated as safe and feasible for the first time in a prospective and
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15
16 100 standardized cohort of patients with Guillain-Barré syndrome (GBS).

17
18 101 3. The intrinsic limitations of this study are its non-randomized, single arm nature, which is
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20 102 conducted in a single center with a limited sample size of GBS patients.

21
22 103 4. Clinical efficacy of SVPE on patients with GBS was a secondary end-point assessment
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24 104 and therefore deserves a randomized controlled trial in future to assess the clinical
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26 105 efficacy of SVPE for the patients with GBS.
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107 **Introduction**

108 Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy with a
109 yearly incidence of 1.2 to 2.3 cases per 100,000 per year¹. GBS is characterized by rapidly
110 progressive limb weakness and, in a proportion of cases, respiratory failure (25%) or severe
111 autonomic dysfunction (10%). Plasma exchange (PE) was the first treatment proven to be
112 effective for GBS, if given within 4 weeks of the onset of weakness²⁻¹⁰. Later studies showed
113 treatment with intravenous immunoglobulin (IVIg) (0.4 g/kg per day for 5 days) has a similar
114 efficacy as PE in patients with GBS who are unable to walk, if started within 2 weeks of the onset
115 of weakness^{11,12}.

116
117 Unfortunately, most patients in low-income countries cannot afford expensive treatment with
118 either PE or IVIg¹³. In Bangladesh, a full course of IVIg for a 60 kg adult costs approximately
119 12,000-16,000 US\$ and treatment with conventional PE for 5 days costs approximately 4,500-
120 5,000 US\$. The mean income in Bangladesh was 4 US\$ per day in 2016 (World Bank and
121 Bangladesh Bureau of Statistics 2016); IVIg and PE cost the equivalent of 3,000 and 1,250 mean
122 income days, respectively. At present, the majority (92%) of patients with GBS in Bangladesh
123 receive supportive care only¹³. In addition, mobile PE equipment is not available in Bangladesh;
124 therefore, patients admitted to the intensive care unit (ICU) cannot receive PE. We previously
125 reported the mortality rates for GBS in Bangladesh range from 12 to 14% and observed 29% of
126 patients with GBS in Bangladesh are unable to walk at 6 months after onset; these poor outcomes
127 are undoubtedly due to the low rates of specific treatment with PE or IVIg^{14,15}.

128
129 Small volume plasma exchange (SVPE) may represent a cheap, effective alternative treatment for
130 GBS. SVPE is based on the same principle as conventional PE (selective removal of plasma) but
131 uses a novel, simple technique with much lower costs (approximately 500 US\$). The current non-

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3 132 randomized trial was designed to investigate the safety and feasibility of SVPE in 20 patients
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5 133 with GBS admitted to the National Institute of Neurosciences Hospital in Dhaka, Bangladesh.

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9 135 **Methods/Design**

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11 136 Study design

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14 137 For this non-randomized, single arm, interventional safety and feasibility trial, 20 adult patients
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16 138 with GBS were enrolled between March 2016 and December 2016 for SVPE at the National
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18 139 Institute of Neurosciences and Hospital (NINS), Dhaka, Bangladesh. A detailed study protocol
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20 140 was published previously and includes definitions of all variables used in this study¹⁶.

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24 142 Four to six daily sessions of whole blood sedimentation and removal of supernatant plasma after
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26 143 re-transfusion of the sedimented blood cells was planned for the 20 patients with GBS, with a
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28 144 target of removing an overall volume of at least 8 litres (L) of plasma over a total of 8 days¹⁶.
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30 145 (See supplementary video for SVPE procedure)

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35 147 Patients with GBS were monitored according to a standard protocol throughout the course of
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37 148 SVPE until the second day after withdrawal of the central venous catheter (CVC) in order to
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39 149 assess predefined measures of safety and feasibility and followed up for six months to assess
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41 150 neurological outcome. The protocol was reviewed and approved by the institutional research and
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43 151 ethics review committees at the icddr,b and registered at clinicaltrials.gov (NCT02780570)¹⁶. All
44
45 152 patients provided written informed consent to participate in this study.

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50 154 Patient and Public Involvement

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52 155 Patients and or public were not involved either in the development of the research question, study
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54 156 design and outcome measure or recruitment to and conduct of the study.

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3 157 *Inclusion and exclusion criteria for patients with GBS*
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5 158 Patients aged ≥ 18 -years-old fulfilling the diagnostic criteria for GBS of the National Institute of
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7 159 Neurological and Communicative Disorders and Stroke (NINDS) ¹⁷ were enrolled, provided they
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9 160 were unable to walk unaided for more than 10 meters (GBS disability score ≥ 3), presented
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11 161 within 2 weeks of the onset of weakness, and were unable to afford standard treatment with IVIg
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13 162 or PE. Patients with concomitant severe or terminal illnesses, evidence of healthcare-associated
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15 163 infection (HAI) on admission (except for aspiration pneumonia), a previous history of severe
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17 164 allergic reactions to properly matched blood products, and pregnant women were excluded from
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19 165 the study.
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24 167 *Control cohort*
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26 168 To compare the safety of SVPE in patients with GBS in the context of the background risk of
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28 169 central line-associated blood stream infection (CLABSI) at our institution, we prospectively
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30 170 assessed the incidence of CLABSI in a hospital control group of 24 adult patients without GBS
31
32 171 receiving neurocritical care. Hospital controls were eligible based on the following
33
34 172 characteristics: ≥ 18 -years-old, a neurological diagnosis other than GBS, and a CVC placed for $>$
35
36 173 2 and ≤ 8 calendar days after admission to the same ICU or HDU unit as the SVPE-treated
37
38 174 patients. Patients with a HAI (except aspiration pneumonia) and pregnant women were excluded
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40 175 from the control group.
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46 177 *Primary and secondary outcome measures*
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48 178 The primary outcome measures of safety were the number of patients with GBS treated with
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50 179 SVPE who developed either severe sepsis or septic shock due to CLABSI ¹⁸ and the occurrence
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52 180 of venous thrombosis in the limb where the CVC was placed. The primary outcome measure of
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54 181 feasibility was the ability to remove at least 8 L of plasma over 8 days.
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3 182 The secondary outcome measures of the safety of SVPE were the relative risk of CLABSI due to
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5 183 SVPE (compared to CLABSI in the hospital control group without GBS), hemodynamic
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7 184 instability during the SVPE procedure, and development of anaemia (Hb < 8 gm/dL) or any
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9 185 catheter-related haemorrhage requiring a blood transfusion.
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11 186 The secondary outcome measure of feasibility of SVPE was the rate of CVC occlusion during the
12
13 187 SVPE procedure. In addition, neurological outcome was assessed using the GBS disability score
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15 188 ¹⁹, MRC sum score ²⁰, Overall Neuropathy Limitation Scale (ONLS) ²¹ and Rasch-built Overall
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17 189 Disability Scale (R-ODS) ²² at 1st, 2nd, 3rd, and 6th months from the start of SVPE.
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22 191 Procedure safety and documentation

23
24 192 Strict aseptic procedures were followed to prevent CLABSI ²³⁻²⁵. SVPE was documented in terms
25
26 193 of the duration and amount of plasma removed in each session, and the type and volume of
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28 194 replacement fluid and fresh frozen plasma (FFP) used. Throughout the procedure, the
29
30 195 haemodynamic, haematological, biochemical, coagulation and infection profiles of the SVPE-
31
32 196 treated patients were monitored according to the protocol ¹⁶. Screening for hepatitis B and C
33
34 197 viruses, human immunodeficiency virus (HIV) and syphilis were performed as patient baseline
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36 198 assessments, and also on donor FFP before administration. CLABSI, primary and secondary
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38 199 bloodstream infections ¹⁸, catheter-associated urinary tract infection (CAUTI) ²⁶, ventilator-
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40 200 associated pneumonia (VAP) ²⁷ and other HAI ^{28,29} were documented in the SVPE-treated
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42 201 patients with GBS and the hospital control group.
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47 203 Sample size

48 204 This safety and feasibility study enrolled 20 patients with GBS for SVPE. We could not
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50 205 perform a formal power calculation for this safety and feasibility study. The sample size
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52 206 was based on previous pilot studies conducted in GBS ^{30,31}. The baseline rate of CLABSI
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3 207 was measured in the hospital control group of 24 patients without GBS admitted to the
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5 208 same study facility who required a CVC for at least 8 days during the study period.

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9 210 Stopping rules for the trial based on safety and feasibility

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11 211 Decision to stop the SVPE trial was designated using a Bayesian approach³²⁻³⁴.

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13 212 Accordingly, a predictive success rate of 75% was predefined for the SVPE procedure. If
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15 213 more than 5 of 20 patients experienced an SAE, or if it appeared impossible to remove at
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17 214 least 8 L of plasma over 8 days in at least 15 of 20 patients, the procedure was considered
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19 215 unsafe or unfeasible.

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24 217 Statistical analysis

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26 218 The rate of HAIs (CLABSI, VAP and CAUTI) per 1000 device days were calculated by
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28 219 dividing the number of each HAI during the study period by the number of device days and
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30 220 multiplying the result by 1000. The infection safety profile for SVPE was assessed by
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32 221 calculating the standardized infection ratio to define the risk of HAIs in patients with GBS
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34 222 treated with SVPE. The standardised infection ratio (SIR) was calculated by dividing the
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36 223 number of observed HAI by the number of HAI predicted (i.e., the infection rate in the control
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38 224 group). The predicted HAI rate was calculated using the rates of HAI in the hospital control
39
40 225 group of patients without GBS during the study period. Percentage values were compared using
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42 226 the Chi-square test or Fisher's exact test (two-tailed) and median values, the Mann-Whitney U-
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44 227 test using SPSS 22 software (IBM SPSS Statistics for Windows Version 22.0., IBM Corp.,
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46 228 Armonk, NY, USA). Analyses were performed on an intention-to treat basis. All *P*-values
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48 229 reported are two-sided; $p < 0.05$ was considered significant.

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231 **Results**

232 Patients and hospital controls

233 The demographic and clinical characteristics of the 20 patients with GBS are given in Table 1.

234 The median age of the patients with GBS was 33 years (range; 18-55); median body weight was

235 60 kg (IQR, 55-65 kg; range, 50-72 kg) and 13 (65%) patients were male (Fig. 1). On admission

236 and before the start of SVPE, all 20 patients with GBS were unable to walk independently (GBS

237 disability score, 4). One patient required mechanical ventilation from the second day after the

238 onset of weakness; SVPE was started on the fourth day of mechanical ventilation (patient 9, Fig.

239 1). Two of the 19 patients who did not require mechanical ventilation at the start of the study

240 required mechanical ventilation on the second day after initiation of SVPE (patients 11 and 19,

241 11 and 2 days after the onset of weakness, respectively; Fig. 1). The median MRC sum score for

242 the limb muscles in all 20 patients was 20 (IQR: 0-29; range: 0-36; Fig. 1). Symptoms of a

243 preceding infection in the 4 weeks before the onset of weakness were present in 18 (90%)

244 patients with GBS, of whom 10 (50%) had diarrhoea. Median duration from admission to start of

245 SVPE was two days (IQR, 2-3 days; range, 0-7 days). Median duration to nadir from the onset of

246 weakness was five days (range, 1-13 days). Electrodiagnostic nerve conduction studies indicated

247 15 (75%) patients had an axonal subtype and 5 (25%) patients had a demyelinating subtype of

248 GBS. Median duration from onset of weakness to NCS examination was 10 days (range, 4-16

249 days). All patients had albuminocytologic dissociation; median CSF protein was 166 mg/dL

250 (range 117-253 mg/dL). Median duration from onset of weakness to CSF examination was 11

251 days (range, 4-17 days).

252

253 Median age of the 24 hospital control patients without GBS was 44 years (IQR, 25-57; range; 18-

254 74); 10 (42%) were male. Age and gender distribution were not significantly different compared

255 to the 20 patients with GBS ($p = 0.2155$, $p = 0.1434$, respectively). The diagnoses for these 24

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3 256 patients were: brain tumour ($n = 5$), transverse myelitis ($n = 5$), head trauma after road traffic
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5 257 accident ($n = 3$), viral meningoencephalitis ($n = 2$), myasthenia gravis ($n = 2$), compressive
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7 258 cervical myelopathy ($n = 2$), cerebrovascular accident ($n = 2$), motor neuron disease ($n = 1$),
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9 259 electrolyte imbalance ($n = 1$) and status epilepticus ($n = 1$).
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14 261 Primary endpoints

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16 262 One patient with GBS treated with SVPE developed severe sepsis, possibly due to SVPE-related
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18 263 CLABSI (SVPE window-period blood culture revealed methicillin-resistant *Staphylococcus*
19
20 264 *aureus*). This patient required intravenous fluid, noradrenalin infusion and intravenous
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22 265 antibiotics, but eventually improved (patient 11, Fig. 1). This patient also had signs and
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24 266 symptoms suggestive of aspiration pneumonia and VAP; *Streptococcus spp.* was isolated from
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26 267 pulmonary aspirates. Further laboratory results revealed dys-electrolytemia, anaemia and hypo-
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28 268 albuminemia. No patients experienced deep vein thrombosis due to the CVC for SVPE. Fifteen
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30 269 (75%) of the 20 patients met the primary endpoint of feasibility, defined as the ability to remove
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32 270 at least 8 L of plasma in eight days. The median volume of plasma removed was 8.5 L (IQR, 7.9-
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34 271 8.8 L; range, 6.3-9.6 L; Fig. 1). The median plasma exchange rate was 140 mL/kg bodyweight
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36 272 (IQR, 125-155 mL/kg; range, 110-175 mL/kg) over 8 days and 16 (80%) patients had a plasma
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38 273 exchange rate > 120 mL/kg (Table 2).
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44 275 Secondary endpoints

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46 276 *Infections among SVPE-treated patients with GBS and hospital controls*

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48 277 Among the 20 patients with GBS treated with SVPE, six (30%) had fever during SVPE (Fig. 1,
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50 278 Supplementary Figure 1), including 2 (10%) patients with leucocytosis who were diagnosed with
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52 279 HAI (VAP and CAUTI in one patient; VAP in one patient). In three out of four (20%) patients
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54 280 with fever without leucocytosis, fever subsided within two to three days without antimicrobial
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3 281 therapy (Fig. 1). The remaining patient with pyrexia without leucocytosis had microbiological
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5 282 evidence of both CLABSI and VAP (patient 11, Fig. 1). In all other 14 patients with GBS, no
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7 283 fever was documented during the course of SVPE until the tenth day of SVPE (second day after
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9 284 removal of the CVC for SVPE). Five of these 14 patients had leucocytosis, but no site-specific
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11 285 HAI could be detected. However, one of the nine patients without fever but leucocytosis fulfilled
12
13 286 the criteria for CAUTI (patient 12, Fig. 1). All three patients who required mechanical ventilation
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15 287 subsequently developed VAP; two of the 13 patients who required a urinary catheter developed a
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17 288 CAUTI (patient 11, Fig. 1). No patients died during the 6 months follow-up.
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22 290 All 24-hospital control patients without GBS required mechanical ventilation and an indwelling
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24 291 urinary catheter. Of these patients, 22 (92%) patients had fever, of whom 15 (63%) had
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26 292 leucocytosis; a diagnosis of a specific HAI could be made 14 of these 15 patients (CLABSI in
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28 293 two, CAUTI in one, VAP in 11) and four (17%) fulfilled the criteria for severe sepsis
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30 294 (Supplementary Figure 1). Seven (29%) of the 24 hospital control patients had fever without
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32 295 leucocytosis. In two of these seven patients, a specific HAI was diagnosed (CAUTI and VAP in
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34 296 one, and VAP in one). In two hospital control patients, no fever was documented until day 10
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36 297 after first placement of the CVC, but leucocytosis was present and no site-specific HAI could be
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38 298 detected (Supplementary Figure 1).
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42
43 300 The rates of CLABSI, CAUTI and VAP per 1000 device days in the SVPE-treated patients with
44
45 301 GBS were 6.25, 19.2 and 40 compared to 10.4, 10.4 and 67.7 for the hospital control patients
46
47 302 without GBS, respectively. The relative risks of CLABSI, CAUTI and VAP associated with
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49 303 SVPE were 0.6, 1.2 and 1.8, respectively, compared to hospital control patients. The rates of
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51 304 CLABSI, CAUTI and VAP were comparable between SVPE-treated patients with GBS and
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53 305 hospital control patients ($p > 0.05$). Antimicrobial agents were used more frequently in the
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3 306 hospital control patients ($p < 0.0001$; Fig. 2). The standardised infection ratios for CLABSI,
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5 307 CAUTI and VAP for SVPE-treated patients with GBS were 0.6, 1.8 and 1.9, respectively.
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9 309 *Other secondary endpoints*

11 310 Ten (50%) of the 20 patients treated with SVPE experienced transient hypotension during SVPE,
12
13 311 which was corrected by infusion of 200-300 mL crystalloid saline (Fig. 1). Minor bleeding
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15 312 through the CVC insertion site (excluding at the time of insertion) was observed in 10/20 patients
16
17 313 (50%; Fig. 1); these bleeds required a pressure pack. Reduction of the anticoagulant dose along
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19 314 with a pressure pack was required in 3/20 patients, who all had a prolonged prothrombin time
20
21 315 (PT). Three patients had single episode of haemorrhage through the urinary catheter: one was
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23 316 diagnosed with a CAUTI with normal coagulation profile, one had a prolonged PT, the other had
24
25 317 sterile haematuria with normal PT. Overall, PT and activated partial thromboplastin time (aPTT)
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27 318 were prolonged in 4/20 patients and only PT was prolonged in 2/20 patients. Clotting time and
28
29 319 bleeding time were not prolonged in any patient. One patient developed anaemia (haemoglobin, 8
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31 320 gm/L) at the end of SVPE; this patient also had severe sepsis and required one unit of blood
32
33 321 transfusion (patient 11, Fig. 1). CVC blockages were not observed in any SVPE-treated patients
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35 322 with GBS. One patient with increased clotting tendency who required an increased dose of low
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37 323 molecular weight heparin had shortened clotting time (CT) ($< 50\%$ of upper limit of normal),
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39 324 though PT was normal (patient 10, Fig. 1).
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47 326 The neurological outcomes of the SVPE-treated patients with GBS at six months in terms of
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49 327 neurological scores are given in Table 3. Median time to recover the ability to walk unaided was
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51 328 4 weeks (Fig. 3). Fourteen (70%) of the 20 patients had an improvement in GBS disability score
52
53 329 of one or more grades at four weeks after the onset of SVPE. At one month, 12 patients (60%)
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55 330 were able to walk unaided, two patients (10%) were able to walk aided and six (30%) patients
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3 331 were bedbound, of whom three still required mechanical ventilation. At three months, 14 (70%)
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5 332 patients were able to walk unaided, one (5%) could walk with aid and five (25%) patients were
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7 333 bedbound. At six months, 14 (70%) patients were able to walk unaided, three (5%) could walk
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9 334 with aid and three (15%) remained bedbound (Table 3).

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14 336 *Other relevant clinical and laboratory findings*

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16 337 Allergic/transfusion reaction to FFP was observed in four patients with GBS treated with SVPE
17
18 338 (Fig. 1). These transfusion reactions presented as an itchy erythematous skin rash (three patients),
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20 339 fever (two patients), hypotension (one patient) following transfusion of FFP; all of these reactions
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22 340 were managed with oral antihistamine (and intravenous saline in one patient) without further
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24 341 complications.

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29 343 The other documented haematological and biochemical abnormalities were hypo-albuminemia (n
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31 344 = 4), thrombocytopenia ($n = 6$), hyponatraemia ($n = 1$), hypokalaemia ($n = 3$), hypomagnesaemia
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33 345 ($n = 1$), hypocalcaemia ($n = 3$); (Table 2).

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3 348 **Discussion**

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5 349 Principal findings

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7 350 This study suggests SVPE may represent a safe and feasible alternative to conventional plasma
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9 351 exchange for patients with severe GBS in limited-resource settings. Of the 20 patients in this
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11 352 study, one (5%) experienced a SAE (severe sepsis due to probable CLABSI). The rate of SAE
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13 353 was not significantly higher than the hospital control group without GBS with a CVC, and no
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15 354 patients had a CVC-related thromboembolic event in patients with SVPE. We were able to
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17 355 remove the prespecified target volume (8 L) of plasma as the target primary endpoint of
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19 356 feasibility in 15/20 (75%) patients with GBS. Median plasma exchange volume and rate during
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21 357 SVPE were 8.4 L and 140 mL/kg, respectively. Minor adverse effects included transient
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23 358 hypotension during SVPE in 50% (10/20), minor haemorrhage from CVC insertion site in 50%
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25 359 (10/20), transfusion reaction to fresh frozen plasma in 20% (4/20), and hypo-albuminemia,
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27 360 anaemia and electrolyte imbalance in 20% (4/20) of patients. An improvement of at least one
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29 361 grade on the GBS disability score was observed for 14/20 (70%) patients at four weeks after the
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31 362 initiation of SVPE. No patients died.

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37 364 *Comparison with baseline hospital control patients and standard PE*

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39 365 With respect to HAIs, no significant differences were observed in the frequency of CLABSI,
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41 366 severe sepsis, VAP or CAUTI between the SVPE-treated patients with GBS and 24 hospital
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43 367 control patients without GBS treated using a CVC in the same ICU or HDU (Fig. 2). However,
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45 368 antimicrobial agents were used more frequently, usually prophylactically, in the hospital control
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47 369 patients compared to the patients with GBS treated with SVPE ($p < 0.0001$; Fig. 2). The
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49 370 probability of detecting microorganisms in clinical infections may have been reduced due to
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51 371 overzealous use of antibiotics in the hospital control patients. Early trials of PE in patients with
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53 372 GBS showed 34% of patients develop severe infections^{7, 35}. Subsequently, another large trial

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3 373 documented septicaemia in 19% of patients⁵. However, the rates of CLABSI were not reported.
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5 374 The volume exchanged during SVPE is within the range recommended in the protocol for
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7 375 standard PE [120-200 mL/kg (standard PE) vs. 140 mL/kg for SVPE]⁷. Exchange of 6 L of
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9 376 plasma in adult patients is clinically beneficial, but less effective than exchange of 12 L;
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11 377 exchanging 18 L provides no added benefit⁵. This suggests that the correlation between clinical
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13 378 benefit and the volume of plasma removed is not linear and exchanging more than 6 L of plasma
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15 379 is likely to have a beneficial effect. We were able to remove >120 mL/kg plasma in 80% of
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17 380 patients, which should provide a therapeutic effect³⁶. Notably, the body weight of our patients
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19 381 may be lower than that of patients in western countries. In addition, SVPE was complete within 8
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21 382 days, shorter than the usual time required for a full session of PE (10 to 12 days).
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23 383
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25 384 Important observations in terms of secondary endpoints were transient hypotension, transfusion
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27 385 reaction to FFP and minor bleeding through the CVC insertion site. Hypotension is a common
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29 386 complication during traditional PE that affects nearly half of patients⁵. Spells of hypotension
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31 387 during SVPE were more frequent during the three to four days after initiation of SVPE, and could
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33 388 be easily corrected by rapid infusion of 300-400 mL saline (Fig. 1). The hypotension could
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35 389 possibly be explained by hypovolemia due to drawing blood or as a result of the compromised
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37 390 autonomic nervous system in patients with GBS. As SVPE proceeded, hypotensive spells were
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39 391 encountered less frequently despite drawing the same volume of blood, which may in part be
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41 392 explained by adaptation of the vasomotor system or recovery from autonomic dysfunction. Minor
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43 393 bleeding through the CVC insertion site occurred in 50% of patients and could be controlled by
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45 394 applying a simple pressure pack over the CVC insertion site in most cases; mild prolonged PT
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47 395 was noted in 30% (3/10) patients. However, spontaneous bleeding usually occurs if the PT is
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49 396 more than 2.5 times prolonged and PC is < 0.50 lac/ μ L³⁷. Movement of the limb where the CVC
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51 397 was placed may have caused traction on the CVC and contributed to local bleeding in the other
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3 398 seven patients. Haematuria is not uncommon in patients with a UTI, as may have occurred in one
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5 399 SVPE treated patient; traumatic traction of the urinary catheter may cause haematuria in two
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7 400 other catheterized SVPE-treated patient taking oral aspirin, who had haematuria and sterile urine.
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9 401 We also monitored the major organ function and biochemical status of the patients treated with
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11 402 SVPE. No patients experienced hepatic or renal impairment. One patient developed anaemia and
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13 403 hypoalbuminemia; this patient had severe sepsis, a common cause of anaemia and
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15 404 hypoalbuminemia in critically ill patients admitted to an ICU (patient 11, Fig. 1). Electrolyte
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17 405 imbalances were detected in 15% of the SVPE-treated patients with GBS, and were mild,
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19 406 subclinical and easily corrected.
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24 408 The median reported durations to recovery of independent walking in patients with GBS in large-
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26 409 scale RCTs after PE are 53, 52 and 70 days^{4, 5, 7}; compared to 30 days in our patients treated with
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28 410 SVPE. Moreover, 60% of the patients with GBS treated with SVPE were able to walk
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30 411 independently at four weeks, whereas 20% of patients with GBS acquired independent walking
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32 412 ability at four weeks after traditional PE³⁵. However, these differences may possibly may be due
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34 413 to the small sample size and variations in demographic and neurophysiological characteristics
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36 414 between cohorts. Finally, SVPE was completed in all 20 patients and no patients died.
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416 *Limitations of SVPE*

417 SVPE is a time-consuming and labour-intensive procedure, which is a limitation. We used
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43 418 multiple thin-lumen tubing systems interconnected with a multichannel connector device, which
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45 419 may increase the chance of blood coagulating within the tubing system. Coagulation may require
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47 420 manipulation or replacement of the tubing to ensure free flow of blood and saline. Such handling
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49 421 could increase the chance of microbial contamination. A single continuous wide-lumen tubing
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51 422 system (SVPE kit) could resolve this problem. Most importantly, personnel conducting the SVPE
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3 423 procedure should maintain proper aseptic technique, which can sometimes be challenging in
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5 424 developing countries. Furthermore, other adaptations such as provision of a larger blood bag or
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7 425 increasing the number of days for SVPE could be considered to increase the plasma exchange
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9 426 rate.

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13 428 *Clinical implications and future research*

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15 429 Despite the limitations, our study showed SVPE is a safe and feasible treatment for GBS in a
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17 430 resource-limited setting where IVIg or PE are either unavailable or unaffordable. Specifically, the
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19 431 poorest 20% of the world's population (1.8 billion people) who typically earn less than 10 US\$
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21 432 per day and who are not covered by a national health insurance system may benefit. Considering
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23 433 the incidence of GBS is 2/100,000 in developing countries, approximately 40,000 patients could
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25 434 potentially benefit from SVPE every year, worldwide. In the future, a multicentre RCT is
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27 435 required to assess the clinical efficacy of SVPE for patients with GBS. If proven effective, SVPE
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29 436 could be an affordable and easily available alternative plasma exchange technique in low-income
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31 437 countries for patients with GBS and other disorders, who at present cannot afford standard PE
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33 438 due to its high cost and unavailability.

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3 440 **Declarations**
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26
27 450 size of the study. MV, MVJ, SR, and HPE contributed to the infection safety guidelines in the
28
29 451 study design. BI and QDM conducted the study and BI collected and analysed the data and
30
31 452 drafted the manuscript. All authors have critically revised the manuscript and have read and
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33 453 approved the final manuscript.
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51 460 analysis, data interpretation, or writing of the report.
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5 464 interests that may have influenced the findings described in this manuscript to disclose.
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11 467 comprised of an Ethical Review Committee (ERC) and Research Review Committee (RRC),
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13 468 reviewed and approved this study protocol on 09/12/2015 (reference number: PR-15086, version
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15 469 no 3).
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20 471 Data sharing: The dataset is available from the lead author on request.
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22 472

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24 473 Transparency: The corresponding author affirms that the manuscript is an honest, accurate and
25
26 474 transparent account of the study being reported; that no important aspects of the study have been
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28 475 omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have
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30 476 been explained.
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3 595 Table 1: Demographic and clinical characteristics of the 20 patients with GBS included in this
4 596 small volume plasma exchange (SVPE) study at entry
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Characteristic	Value
Demography	
Sex [males: females (ratio)]	13:7 (1.85)
Age (years) ¶	33 (18 - 55)
Body weight (kg) ¶	60 (50 - 72)
Antecedent events ‡ (total)	18 (90%)
Diarrhoea	10 (50%)
Respiratory infection	5 (25%)
Fever	3 (15%)
Days from antecedent events to weakness ¶	7 (3 - 30)
Days between onset of weakness to admission ¶	7 (2-12)
Neurological deficits at entry	
Weakness in arms and legs	20 (100%)
Cranial nerve deficits	12 (60%)
Decreased deep tendon reflexes	20 (100%)
Sensory involvement	5 (25%)
GBS disability score §	4 19 (95%)
	5 1 (5 %)
Severity of weakness (MRC sum-score) ¶	20 (0-29)
Autonomic dysfunction	11 (55%)

44 598 ¶ Median (range); † increased protein level (> 45 mg/dL) in combination with CSF cell count <
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46 599 50/µL; CSF = cerebrospinal fluid; NCS = nerve conduction study; ‡ symptoms of an infection in
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48 600 the four weeks preceding the onset of weakness; § GBS disability score (0 - 6) = 0: healthy state;
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50 601 1: minor symptoms and capable of running; 2: able to walk 10 meters or more without assistance
51
52 602 but unable to run; 3: able to walk 10 meters across an open space with help; 4: bedridden or
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54 603 chair-bound; 5: requiring assisted ventilation for at least part of the day; 6: dead.

604 Table 2: Treatment characteristics and complications associated with SVPE in the 20 patients
605 with GBS

Characteristic/complication	Value
<i>Treatment characteristics</i>	
Number of sessions of SVPE per patient [¶]	30 (24 - 42)
Volume of plasma removed per patient [¶]	8.4 (6.3 – 9.6)
Plasma exchange rate (mL/kg) [¶]	140 (110-175)
Time between hospital admission and SVPE (days) [¶]	8 (5-10)
Time between onset of weakness and start of SVPE (days) [¶]	8 (5-10)
Need to stop SVPE due to poor hemodynamic tolerance	0/20 (0%)
Need for blood transfusion for anaemia	1/20 (5%)
Reduction of anticoagulant drug dose for bleeding	3/20 (15%)
Temporary withdrawal of antiplatelet drug for bleeding	4/20 (20%)
Increased anticoagulant drug dose to continue SVPE	1/20 (5%)
CVC blockade/replacement	0/20 (0%)
<i>Complications during SVPE</i>	
<i>Infection</i>	
Leukocytosis	7/20 (35%)
CLABSI [§]	6.25
VAP [§]	136.4
CAUTI [§]	40
Severe sepsis	1/20 (5%)
Antimicrobial agents used	6/20 (30%)
<i>Bleeding and coagulation</i>	
Bleeding from CVC insertion site	10/20 (50%)
Bleeding from mucosal area	3/20 (15%)
Prolonged BT (BT > 10 min)	0/20 (0%)
Prolonged CT (CT > 15 min)	0/20 (0%)
Prolonged PT (PT > 14 sec) [¶]	6/20 (30%) [15-19 sec]

Prolonged aPTT (aPTT > 40 sec) [¶]	3/20 (15%) [51-240 sec]
<i>Other complications</i>	
Saline responsive hypotension	10/20 (50%)
Anaemia (Hb < 8 gm/L)	2/20 (10%)
Thrombocytopenia (PC < 1.5 lac/ μ L) [¶]	6/20 (30%) [0.79-1.3 lac/ μ L]
Jaundice (serum bilirubin > 1.2 mg/dL)	0/20 (0%)
Renal impairment (serum creatinin > 1.2 mg/dL)	0/20 (0%)
Hyponatraemia (serum Na ⁺ < 135 mEq/L)	1/20 (5%) [126 mEq/L]
Hypokalaemia (serum K ⁺ < 3.5 mEq/L) [¶]	3/20 (15%) [2.6-3.2 mEq/L]
Hypoalbuminemia (serum albumin > 35 gm/L) [¶]	4/20 (20%) [26-32 gm/L]
Hypocalcaemia (serum Ca ⁺ < 2.2 mmol/L) [¶]	3/20 (15%) [1.89-1.98 mmol/L]
Hypomagnesaemia (serum Mg ⁺ < 75 mEq/L) [¶]	1/20 (5%) [73 mEq/L]
Hypersensitivity/transfusion reaction to FFP	4/20 (20%)

606

607 ¶ Median (range); § rate per 1000 device days; CLABSI: central line-associated bloodstream
608 infection; VAP: ventilator-associated pneumonia; CAUTI: catheter-associated urinary tract
609 infection; CVC: central venous catheter; BT: bleeding time, CT: clotting time; PT: prothrombin
610 time; APTT: activated partial thromboplastin time; FFP: fresh frozen plasma.

611

612 Table 3: Neurological outcomes of the 20 patients with GBS after SVPE
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Clinical outcome	1 month	2 months	3 months	6 months
Cranial nerve involvement	7/20 (35%)	6/20 (30%)	4/20 (20%)	2/20 (10%)
Autonomic involvement	3/20 (15%)	3/20 (15%)	0/20 (0%)	0/20 (0%)
Sensory dysfunction	1/20 (5%)	1/20 (5%)	1/20 (5%)	1/20 (5%)
GBS disability score [¶]	0 = 0	0 = 1	0 = 1	0 = 2
	1 = 3	1 = 6	1 = 7	1 = 7
	2 = 9	2 = 6	2 = 6	2 = 5
	3 = 2	3 = 1	3 = 1	3 = 3
	4 = 3	4 = 5	4 = 5	4 = 3
	5 = 3	5 = 1	5 = 0	5 = 0
MRC sum score † *	47 (0-60)	49 (0-60)	53 (6-60)	58 (22-60)
ONLS ‡ *	4 (1-12)	3 (0-12)	3 (0-12)	2 (0-10)
R-ODS § *	26 (0-41)	33 (0-45)	37 (0-45)	38 (0-46)

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615 * Median (range); ¶ GBS disability score (0 - 6) = 0: healthy state, 1: minor symptoms and
616 capable of running, 2: able to walk 10 meters or more without assistance but unable to run, 3:
617 able to walk 10 meters across an open space with help, 4: bedridden or chair-bound, 5: requiring
618 assisted ventilation for at least part of the day, 6: dead; † MRC sum score: Medical Research
619 Council sum score; ‡ ONLS: Overall Neuropathy Limitation Scale²¹; § R-ODS: Rash-built
620 Overall Disability Score²²

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3 631 **Figure 1:** Feasibility of SVPE and associated complications for the 20 individual patients with
4 632 GBS.

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9 634 SVPE: small volume plasma exchange, HAI: hospital acquired infection, V: ventilator-associated
10 635 pneumonia, B: central line-associated blood stream infection, U: catheter-associated urinary tract
11 636 infection, ^A measured in litres, ●: spell of hypotension (systolic BP < 90 mm Hg), ◊ : CVC
12 637 insertion site bleeding, ▲: hypersensitivity to fresh frozen plasma, shaded squares: pyrexia due to
13 638 bacterial infection, dotted squares: pyrexia due to suspected viral infection, M: onset of mechanical
14 639 ventilation, C: urinary catheterization.

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23 642 **Figure 2:** Hospital-acquired infections and use of antibiotics in the 20 patients with GBS receiving
24 643 SVPE compared to the 24 hospital control patients without GBS treated in an ICU with a CVC who
25 644 did not receive SVPE.

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29 646 ■ SVPE ($n = 20$): twenty patients with GBS aged ≥ 18 -years-old who were bedbound (GBS
30 647 disability score ≥ 4) received small volume plasma exchange (SVPE) within 2 weeks of the onset
31 648 of weakness. □ Non-SVPE ($n=20$): twenty-four patients aged ≥ 18 -years-old with a diagnosis
32 649 other than GBS who required a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU
33 650 and HDU units in the same period as the patients with GBS received SVPE; * $p < 0.0001$.

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41 653 **Figure 3:** Kaplan-Meier estimate (with 95% confidence limits) of the cumulative incidence of
42 654 restoration of independent walking ability in patients with GBS treated with SVPE.

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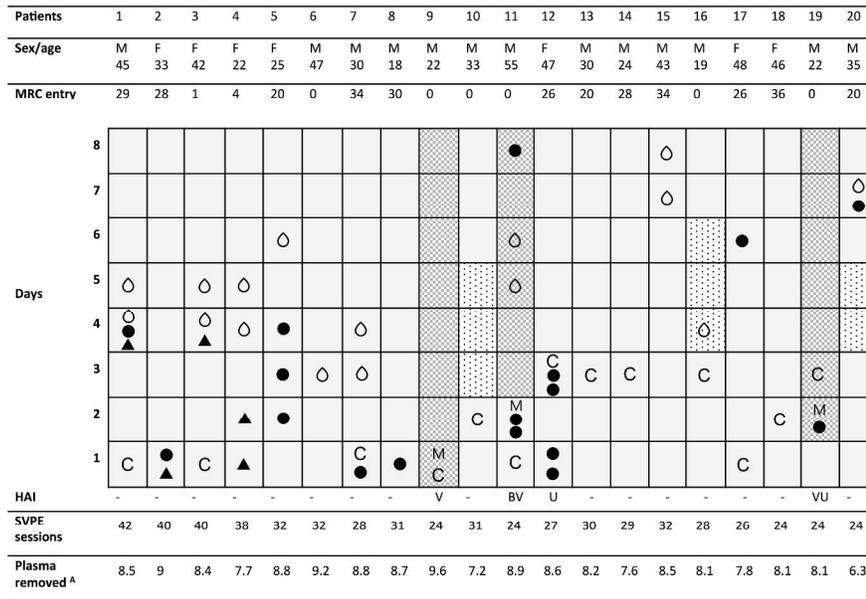


Figure 1: Feasibility of SVPE and associated complications for the 20 individual patients with GBS. SVPE: small volume plasma exchange, HAI: hospital acquired infection, V: ventilator-associated pneumonia, B: central line-associated blood stream infection, U: catheter-associated urinary tract infection, A measured in litres, black dot: spell of hypotension (systolic BP < 90 mm Hg), empty drop: CVC insertion site bleeding, black triangle: hypersensitivity to fresh frozen plasma, shaded squares: pyrexia due to bacterial infection, dotted squares: pyrexia due to suspected viral infection, M: onset of mechanical ventilation, C: urinary catheterization.

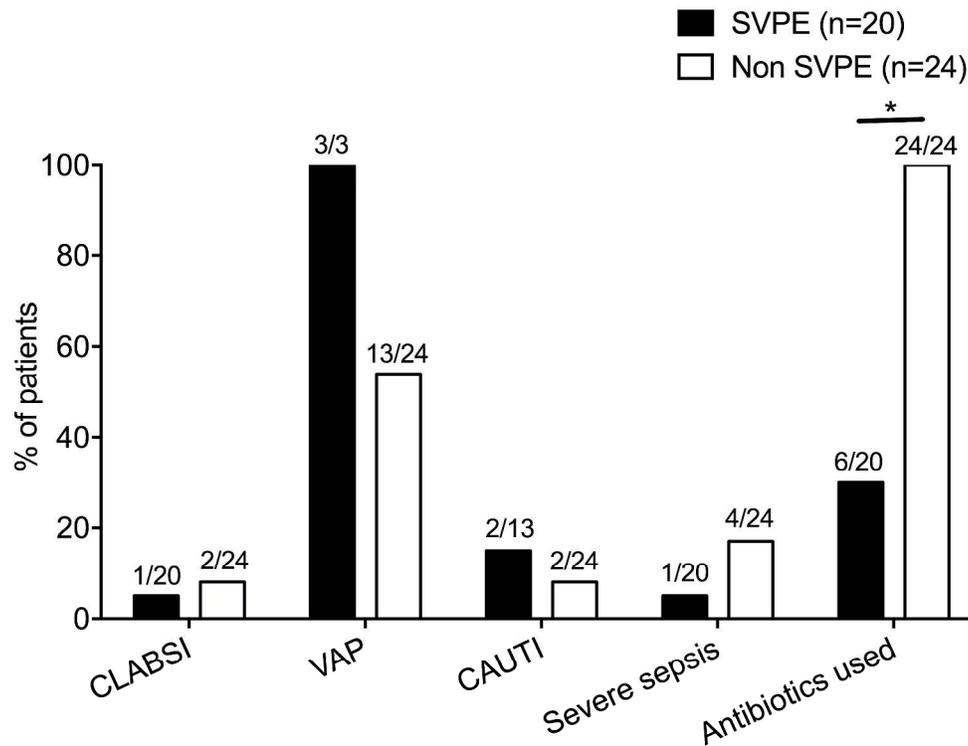


Figure 2: Hospital-acquired infections and use of antibiotics in the 20 patients with GBS receiving SVPE compared to the 24 hospital control patients without GBS treated in an ICU with a CVC who did not receive SVPE.

■ SVPE (n = 20): twenty patients with GBS aged ≥ 18 -years-old who were bedbound (GBS disability score ≥ 4) received small volume plasma exchange (SVPE) within 2 weeks of the onset of weakness. □ Non-SVPE (n=20): twenty-four patients aged ≥ 18 -years-old with a diagnosis other than GBS who required a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period as the patients with GBS received SVPE; * p < 0.0001.

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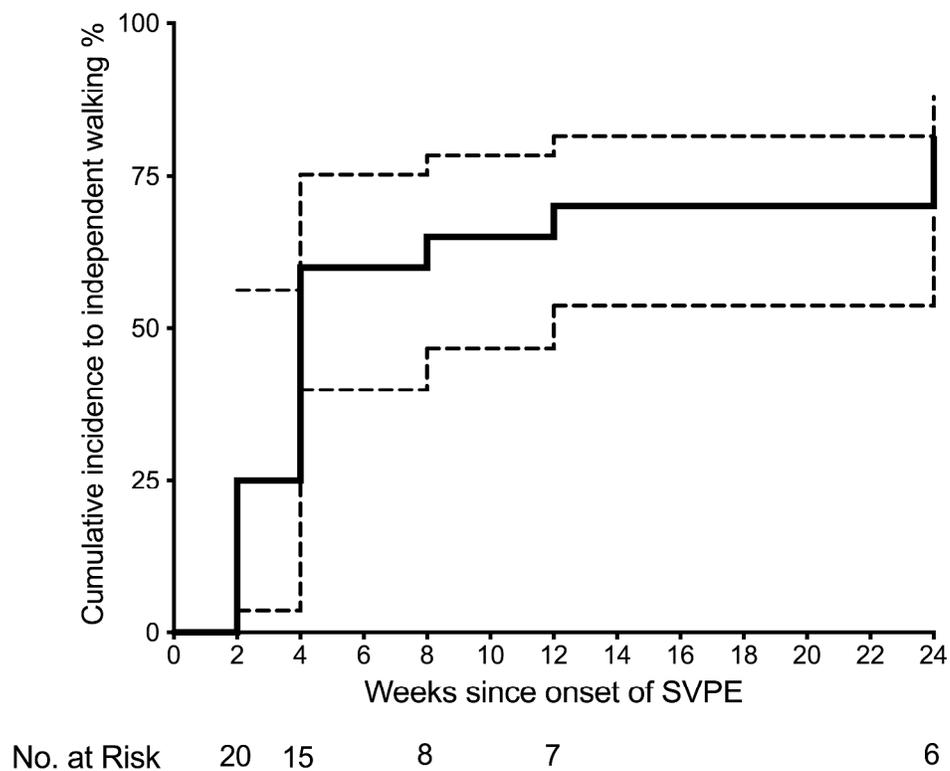
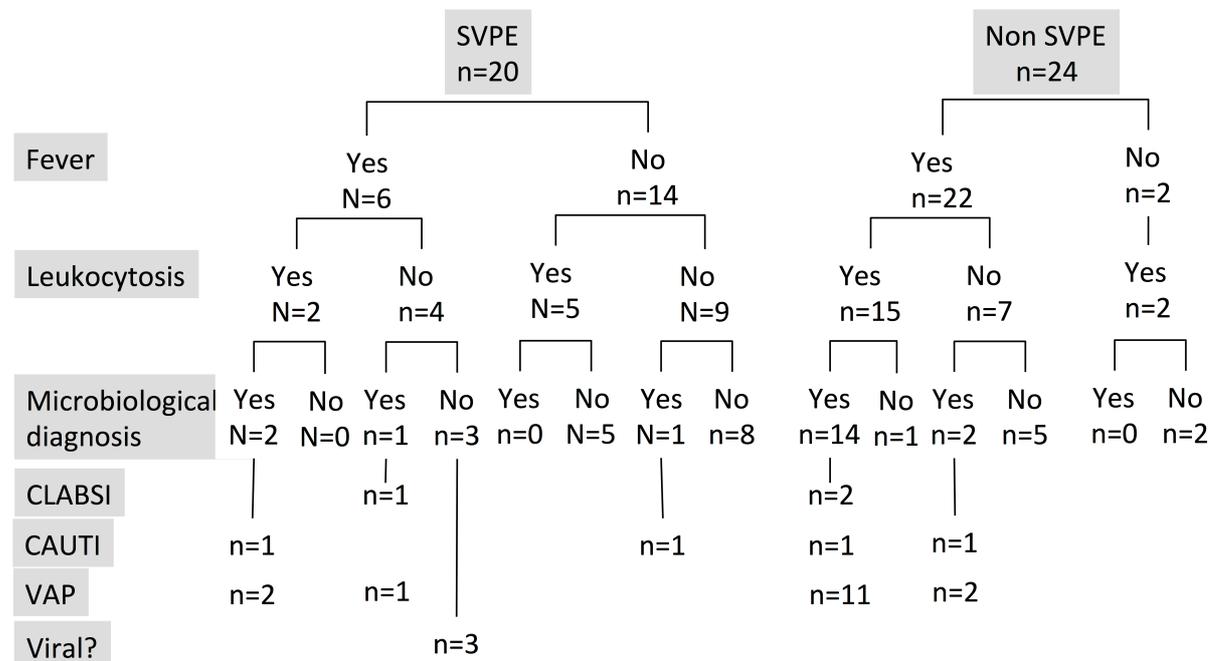


Figure 3: Kaplan-Meier estimate (with 95% confidence limits) of the cumulative incidence of restoration of independent walking ability in patients with GBS treated with SVPE.

Supplementary Figure: Hospital-acquired infections in the 20 patients with GBS treated with SVPE and the 24-hospital control patients without GBS.



SVPE: small volume plasma exchange, CLABSI: central line-associated blood stream

infection, CAUTI: catheter-associated urinary tract infection, VAP: ventilator-associated pneumonia.



Consent form

For a patient's consent to publication of images and/or information about them in BMJ publications.

Name of patient:	<u>ASHRAF ALI</u>
Relationship to patient (if patient not signing this form):	<u>Not applicable</u>
Description of the photo, image, text or other material (Material) about the patient. A copy of the Material should be attached to this form:	<u>Video documentation of the small volume plasma exchange (SVPE) procedure</u>
Provisional title of article in which Material will be included:	Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings: a safety and feasibility study

CONSENT

I ASHRAF ALI (35 years / Male) [PRINT FULL NAME] give my consent for the Material about me/the patient to appear in a BMJ publication.

I confirm that I: (please tick boxes to confirm)

- have seen the video clip about me**
- have read the article to be submitted to BMJ**
- am legally entitled to give this consent.**

I understand the following:

- (1) The Material will be published without my/the patient's name attached, however I understand that complete anonymity cannot be guaranteed. It is possible that somebody somewhere - for example, somebody who looked after me/the patient or a relative - may recognise me/the patient.
- (2) The Material may show or include details of my/the patient's medical condition or injury and any prognosis, treatment or surgery that I have/the patient has, had or may have in the future.
- (3) The article may be published in a journal which is distributed worldwide. BMJ's publications go mainly to doctors and other healthcare professionals but are also seen by many others including academics, students and journalists.
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- (5) The text of the article will be edited for style, grammar and consistency before publication.

Patient consent form 031117

- (6) I/the patient will not receive any financial benefit from publication of the article.
- (7) The article may also be used in full or in part in other publications and products published by BMJ and/or by other publishers. This includes publication in English and in translation, in print, in digital formats, and in any other formats that may be used by BMJ or other publishers now and in the future. The article may appear in local editions of journals or other publications, published in the UK and overseas.
- (8) I can revoke my consent at any time before publication, but once the article has been committed to publication ("gone to press") it will not be possible to revoke the consent.
- (9) This consent form will be retained securely and in confidence by BMJ in accordance with the law, for no longer than necessary.

Please tick boxes to confirm the following:

- I consent to BMJ storing my contact details (including outside of the EEA) for the sole purpose of contacting me, if necessary, in the future.
- Where this consent relates to an article in *BMJ Case Reports*, I have/the patient has had the opportunity to comment on the article and I am satisfied that the comments, if any, have been reflected in the article.

Signed: ASHRAF ALI

Print name: ASHRAF ALI

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Dhaka;
Bangladesh

Email address: ashrafali3972@gmail.com

Telephone no: +880 17 1201 0384

If signing on behalf of the patient, please give the reason why the patient can't consent for themselves (e.g. patient is deceased, under 18 or has cognitive or intellectual impairment). **Not applicable**

Date: 16. 02. 2018

- If you are signing for a family or other group, please tick the box to confirm that all relevant members of the family or group have been informed. **Not applicable**

If the patient is a child aged 7 years or older, they must also confirm their consent: **Not applicable**

Signed: _____ Print name: _____

Date of birth: _____ Date: _____

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10 **Details of person who has explained and administered the form** to the patient or their representative
11 (e.g. the corresponding author or other person who has the authority to obtain consent).
12

13 Signed:_____



14 Print name: Dr Md Badrul Islam

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18 Position:_____

19 **Research Trainee and PhD Fellow**

20 Institution:_____

21 **International Centre for Diarrhoeal**
22 **Disease Research, Bangladesh (icddr,b)**

23 Address:_____

24 **Laboratory Sciences and Services Division**
25 **(LSSD)**

26 **The International Centre for Diarrhoeal**
27 **Disease Research, Bangladesh (icddr,b)**
28 **68, Shaheed Tajuddin Ahmed Sarani,**
29 **Mohakhali, Dhaka-1212, Bangladesh**

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31 bislamdmch@gmail.com

32 Telephone no: +880 17 289 0172

33 Date: 16. 02. 2018

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2017 CONSORT checklist of information to include when reporting a randomized trial assessing nonpharmacologic treatments (NPTs)*.
Modifications of the extension appear in italics and blue.

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
Title and abstract					
	1a	Identification as a randomized trial in the title	NA (Non-randomized)		
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3, 4, 5	Refer to CONSORT extension for abstracts for NPT trials	3, 4, 5
Introduction					
Background and objectives	2a	Scientific background and explanation of rationale	6		
	2b	Specific objectives or hypotheses	6, 7		
Methods					
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7	When applicable, how care providers were allocated to each trial group	NA
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	No changes to methods after trial commencement		
Participants	4a	Eligibility criteria for participants	7, 8	When applicable, eligibility criteria for centers and for care providers	NA
	4b	Settings and locations where the data were collected	7		
Interventions†	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7, 8	Precise details of both the experimental treatment and comparator	7, 8
	5a			Description of the different components of the interventions and, when applicable, description of the procedure for tailoring the interventions to individual participants.	9
	5b			Details of whether and how the interventions were standardized.	8, 9

Cite as: Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40-7.

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
	5c.			Details of whether and how adherence of care providers to the protocol was assessed or enhanced	8, 9
	5d			Details of whether and how adherence of participants to interventions was assessed or enhanced	NA
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8, 9		
	6b	Any changes to trial outcomes after the trial commenced, with reasons	No changes to trial outcomes after the trial commenced		
Sample size	7a	How sample size was determined	9	When applicable, details of whether and how the clustering by care providers or centers was addressed	NA
	7b	When applicable, explanation of any interim analyses and stopping guidelines	10		
Randomization:					
- Sequence generation	8a	Method used to generate the random allocation sequence	NA (Non-randomized)		
	8b	Type of randomization; details of any restriction (such as blocking and block size)	NA (Non-randomized)		
- Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	NA (Non-randomized)		
- Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	NA (Non-randomized)		
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Blinding was not possible	If done, who was blinded after assignment to interventions (e.g., participants, care providers, those administering co-interventions, those assessing outcomes) and how	Blinding was not possible

Cite as: Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40-7.

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
	11b	If relevant, description of the similarity of interventions	7, 8		
	11c			If blinding was not possible, description of any attempts to limit bias	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10	When applicable, details of whether and how the clustering by care providers or centers was addressed	NA
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA		
Results					
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	11	The number of care providers or centers performing the intervention in each group and the number of patients treated by each care provider or in each center	Single center study
	13b	For each group, losses and exclusions after randomization, together with reasons	No losses and exclusions after inclusion		
	13c			For each group, the delay between randomization and the initiation of the intervention	11
	new			Details of the experimental treatment and comparator as they were implemented	11, 12, 13, 14
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7		
	14b	Why the trial ended or was stopped	NA (Trial completed)		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1	When applicable, a description of care providers (case volume, qualification, expertise, etc.) and centers (volume) in each group.	NA
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11		

Cite as: Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40-7.

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12, 13, 14		
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	15		
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12, 13, 14, 15		
Discussion					
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18, 19	In addition, take into account the choice of the comparator, lack of or partial blinding, and unequal expertise of care providers or centers in each group	NA
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	16, 17, 18	Generalizability (external validity) of the trial findings according to the intervention, comparators, patients, and care providers and centers involved in the trial	16, 17, 18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16, 17, 18		
Other information					
Registration	23	Registration number and name of trial registry	4		
Protocol	24	Where the full trial protocol can be accessed, if available	Manuscript reference no: 16		
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	20		

*Additions or modifications to the 2010 CONSORT checklist. CONSORT = Consolidated Standards of Reporting Trials

†The items 5, 5a, 5b, 5c, 5d are consistent with the Template for Intervention Description and Replication (TIDieR) checklist

Cite as: Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. *Annals of Internal Medicine*. 2017 Jul 4;167(1):40-7.

Table: Required documents of the safety and feasibility study of the small volume plasma exchange (SVPE) for Guillain-Barré syndrome patients for the World Health Organization Trial Registration Data Set

	Item/Label	Description
1	Primary Registry and Trial Identifying Number	Clinicaltrials.gov NCT02780570
2	Date of Registration in Primary Registry	May 23, 2016
3	Secondary Identifying Numbers	International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) Protocol Number: PR-15086, Version no. 3, Date: 09/12/2015
4	Source(s) of Monetary or Material Support	GBS/CIDP Foundation International Fondation Mérieux: (Small Grants Program 2015)
5	Primary Sponsor	GBS/CIDP Foundation International
6	Secondary Sponsor(s)	Fondation Mérieux: (Small Grants Program 2014)
7	Contact for public queries	MD. BADRUL ISLAM Email: bislamdmch@gmail.com Telephone no: +880 1712 89 0172 Postal address: Dr. Badrul Islam

		Research trainee and PhD Fellow Laboratory Sciences and Services Division (LSSD) Icddr,b Dhaka, Bangladesh
8	Contact for scientific queries	MD. BADRUL ISLAM Principal Investigator (PI) Email: bislamdmch@gmail.com Telephone no: +880 1712 89 0172 Postal address: Dr. Badrul Islam Research trainee and PhD Fellow Laboratory Sciences and Services Division (LSSD) Icddr,b Dhaka, Bangladesh
9	Public title	Small volume plasma exchange for Guillain-Barré syndrome
10	Scientific title	Small volume plasma exchange for Guillain-Barré syndrome in low-income countries: a safety and feasibility study
11	Countries of Recruitment	Bangladesh
12	Health condition(s) or problem(s) studied	Guillain-Barré syndrome (GBS)
13	Interventions	<u><i>Small Volume Plasma Exchange (SVPE)</i></u> A loading dose of low-molecular weight heparin (1.5 mg/kg) will be given subcutaneously at least two hours

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3 before initiation of SVPE; the same dose will be
4 administered once daily or divided into two equal doses
5 daily for eight days or until SVPE is completed. Whole
6 blood (7 mL/kg body weight) will be drawn from the
7 central venous catheter into the blood transfusion bag
8 in each session. The blood bag will be hung beside the
9 patient for 2.5 h on a saline stand and left
10 uninterrupted to allow plasma and blood cells to
11 separate. The blood cells will be infused back into the
12 patient and plasma will be discarded and replaced with
13 fresh frozen plasma and colloid solution alternately (in
14 equal volumes) via the closed-circuit SVPE kit illustrated
15 in. In case of excessive clotting (bleeding time reduction
16 of > 50% of baseline for that patient), aspirin (600 mg)
17 will be administered orally at least two hours before
18 the next SVPE session and continued thereafter at 150
19 mg orally/day until SVPE is completed. One blood bag
20 will be used each day, with a total of six sessions/day. A
21 total of 48 sessions will be performed over eight days,
22 removing approximately 8000 mL plasma in total.
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39 Central venous catheterized patients without GBS

40 To compare the safety of SVPE in patients with GBS in
41 the context of the background risk of central line-
42 associated blood stream infection (CLABSI) at the study
43 intensive care (ICU) and high-dependency care (HDU)
44 units, the incidence of CLABSI will be assessed in a
45 control group of adult patients with a diagnosis other
46 than GBS admitted to the same ICU and HDU units in
47 the same period of time the patients with GBS will be
48 enrolled for SVPE. We will assess the rate of CLABSI in
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		<p>patients aged ≥ 18-years-old requiring a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units.</p>
14	<p>Key Inclusion and Exclusion Criteria</p>	<p><u><i>Inclusion criteria for SVPE in GBS patients</i></u></p> <ol style="list-style-type: none"> 1. Patients aged ≥ 18-years-old fulfilling the diagnostic criteria for GBS of the National Institute of Neurological and Communicative Disorders and Stroke (NINDS) 2. Unable to walk unaided for more than 10 meters (GBS disability score ≥ 3) 3. Presented within 2 weeks of the onset of weakness 4. Unable to afford standard treatment with IVIg or PE. <p><u><i>Exclusion criteria for SVPE in GBS patients</i></u></p> <ol style="list-style-type: none"> 1. Patients with severe or terminal concomitant illness 2. Evidence of healthcare-associated infection on admission (except for aspiration pneumonia) 3. Previous history of severe allergic reaction to properly matched blood products and pregnant women will be excluded from the study. <p><u><i>Inclusion criteria for patients without GBS</i></u></p> <ol style="list-style-type: none"> 1. Patients aged ≥ 18-years-old 2. Requiring a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period of time the patients with GBS enrolled for SVPE. <p><u><i>Exclusion criteria for patients without GBS</i></u></p>

		<ol style="list-style-type: none"> 1. Patients with healthcare-associated infection present on admission (except aspiration pneumonia) 2. Pregnant women
15	Study type	<p><u>Type of the study:</u> Interventional</p> <p><u>Method of allocation:</u> Non-randomized</p> <p><u>Masking:</u> Non-masked</p> <p><u>Assignment:</u> Parallel arm</p> <ul style="list-style-type: none"> • SVPE in patients with GBS • Rate of CLABSI in patients without GBS <p><u>Purpose:</u> Safety and feasibility of SVPE</p>
16	Date of first enrolment	February 20, 2016
17	Target sample size	<p>SVPE in patients with GBS = 20</p> <p>Rate of CLABSI in patients without GBS = ≥ 20</p>
18	Recruitment status	<p>Completed:</p> <ul style="list-style-type: none"> • Twenty cases of GBS have been successfully treated with SVPE and 24 control cases without GBS have been recruited.
19	Primary Outcome(s)	<p><u>Primary outcome of safety:</u></p> <ol style="list-style-type: none"> 1. Number of patients with GBS treated with SVPE developing severe sepsis or septic shock due to central line associated blood stream infection (CLABSI) as per standard guideline (Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central line-associated Bloodstream Infection); CDC Device-associated Module, BSI. January 2017) 2. Occurrence of venous thrombosis in the limb

		<p>where the CVC is placed. Venous thrombosis will be assessed according to Wells criteria (Philip S. Wells et al. Evaluation of d -Dimer in the Diagnosis of Suspected Deep-Vein Thrombosis; N Engl J Med 2003;349:1227-35)</p> <p><u>Primary outcome of feasibility:</u></p> <ol style="list-style-type: none"> 1. Ability to remove at least eight litres of plasma by SVPE over eight days.
20	Secondary Outcome(s)	<p><u>Secondary outcome of safety:</u></p> <ol style="list-style-type: none"> 2. Relative risk of CLABSI due to SVPE compared to CLABSI in control patients without GBS treated using a CVC 3. Hemodynamic instability during the SVPE procedure (variations in systolic blood pressure greater than 30 mmHg or sudden bradycardia involving a reduction in heart rate by more than 20 beats per min within 30 min of starting SVPE or an increase in heart rate above 120 beats per min) 4. Development of anaemia (Hb <7 gm/dL) or serious haemorrhage requiring blood transfusion. <p><u>Secondary outcome of feasibility:</u></p> <ol style="list-style-type: none"> 1. Rate of CVC occlusion during the SVPE procedure 2. The healthcare personnel's acceptability and

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		<p>satisfaction with the SVPE procedure and any unanticipated events compromising the SVPE procedure as assessed using a standard questionnaire.</p> <p>3. Neurological outcome will be assessed in terms of improvement in GBS disability score and MRC sum score at discharge and up to 4 weeks after entry.</p>
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For peer review only

BMJ Open

Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings: a phase II safety and feasibility study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022862.R1
Article Type:	Research
Date Submitted by the Author:	02-May-2018
Complete List of Authors:	Islam, Md Badrul; International Centre for Diarrhoeal Disease Research Bangladesh, LSSD Islam, Zhahirul; The International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) , Laboratory Sciences and Services Division (LSSD) Rahman, Shafiqur; Uttara Adhunik Medical College, Anaesthesia and Intensive Care Endtz, Hubert; Erasmus University Medical Center, Department of Medical Microbiology and Infectious Diseases; Fondation Merieux Vos, Margreet; Erasmus MC Medical Center Rotterdam, Department of Medical Microbiology and Infectious diseases van der Jagt, Mathieu; Erasmus MC, Department of Intensive Care Van Doorn, Peter; Erasmus University Medical Center, Department of Neurology Jacobs, BC; Erasmus University Medical Center, Departments of Neurology and Immunology Mohammad, Quazi; National Institute of Neuroscience
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Medical management
Keywords:	Guillain-Barré syndrome, Small volume plasma exchange, Safety, Feasibility
<p>Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.</p> <p>SUPPLEMENTARY VIDEO.mp4</p>	

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5 2 Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings:
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7 3 a phase II safety and feasibility study
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3 50 **ABSTRACT**

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5 51 **OBJECTIVE**

6
7 52 To assess the safety and feasibility of small volume plasma exchange (SVPE) as an alternative to
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9 53 standard plasma exchange (PE) or intravenous immunoglobulin (IVIg) for Guillain-Barré
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11 54 syndrome (GBS) patients.

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14 55 **DESIGN**

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16 56 Non-randomized, single arm, interventional trial.

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18 57 **SETTING**

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20 58 National Institute of Neurosciences and Hospital, Dhaka, Bangladesh.

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22 59 **PARTICIPANTS**

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24 60 Twenty adult (>18 years) patients with GBS presented within 2 weeks of onset of weakness who
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26 61 were unable to walk unaided for more than 10 meters.

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29 62 **INTERVENTIONS**

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31 63 SVPE involves blood cell sedimentation in a blood bag and removal of supernatant plasma after
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33 64 blood cells are re-transfused. This procedure was repeated three to six times a day, for eight
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35 65 consecutive days.

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38 66 **OUTCOME MEASURES**

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40 67 Serious adverse events (SAE) were defined as severe sepsis and deep venous thrombosis related
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42 68 to the central vein catheter (CVC) used during SVPE. SVPE was considered safe if less than 5/20
43
44 69 patients experienced a SAE, and feasible if 8 L plasma could be removed within 8 days in at least
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46 70 15/20 patients.

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48 71 **RESULTS**

49
50 72 Median patient age 33 years (IQR 23-46; range 18-55); 13 (65%) were male. Median MRC sum
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52 73 score was 20 (IQR 0-29; range 0-36); three (15%) patients required mechanical ventilation. One
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54 74 patient developed SAE (severe sepsis, possibly related to CVC). Minor adverse effects were

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3 75 transient hypotension in 10 (50%) patients; CVC-associated bleeding in 10 (50%); transfusion
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5 76 reaction to fresh frozen plasma in 4 (20%); and hypo-albuminemia, anaemia or electrolyte
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7 77 imbalance in 4 (20%). Removal of 8 L plasma was possible in 15 (75%) patients. GBS disability
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9 78 score improved by at least one grade in 14 (70%) patients four weeks after SVPE started. No
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11 79 patients died.

13 80 CONCLUSION

15 81 SVPE seems a safe and feasible alternative treatment to standard PE or IVIg for GBS; further
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17 82 studies of clinical efficacy in low-resource developing countries are warranted.
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22 84 TRIAL REGISTRATION

24 85 Clinicaltrials.gov NCT02780570 on May 23, 2016
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3 94 **Strength and limitations of the study:**
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7 96 1. The strength of this study underlies the novel and simple technique of SVPE, which is
8
9 97 much less expensive than conventional immunotherapies (plasma exchange and
10
11 98 intravenous immunoglobulin)

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13 99 2. SVPE is corroborated as safe and feasible for the first time in a prospective and
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15
16 100 standardized cohort of patients with Guillain-Barré syndrome (GBS).

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18 101 3. The intrinsic limitations of this study are its non-randomized, single arm nature, which is
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20 102 conducted in a single center with a limited sample size of GBS patients.

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22 103 4. Clinical efficacy of SVPE on patients with GBS was a secondary end-point assessment
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24 104 and therefore deserves a randomized controlled trial in future to assess the clinical
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26 105 efficacy of SVPE for the patients with GBS.
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107 **Introduction**

108 Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy with a
109 yearly incidence of 1.2 to 2.3 cases per 100,000 per year.¹ GBS is characterized by rapidly
110 progressive limb weakness and, in a proportion of cases, respiratory failure (25%) or severe
111 autonomic dysfunction (10%). Plasma exchange (PE) was the first treatment proven to be
112 effective for GBS, if given within 4 weeks of the onset of weakness.²⁻¹⁰ Conventionally for GBS
113 patients, three to six plasma exchange sessions are done in alternate days targeting removal of
114 nearly 12 litres of patient plasma (approximately 3 litres of plasma at each session) within a span
115 of 9 to 14 days.¹¹ This give rise to the plasma exchange rate of 120 - 200 ml/kg (40-
116 50ml/kg/day). Later studies showed treatment with intravenous immunoglobulin (IVIg) (0.4 g/kg
117 per day for 5 days) has a similar efficacy as PE in patients with GBS who are unable to walk, if
118 started within 2 weeks of the onset of weakness.^{12 13}

119
120 Unfortunately, most patients in low-income countries cannot afford expensive treatment with
121 either PE or IVIg.¹⁴ In Bangladesh, a full course of IVIg for a 60 kg adult costs approximately
122 12,000-16,000 US\$ and treatment with conventional PE for 5 days costs approximately 4,500-
123 5,000 US\$. The mean income in Bangladesh was 4 US\$ per day in 2016 (World Bank and
124 Bangladesh Bureau of Statistics 2016); IVIg and PE cost the equivalent of 3,000 and 1,250 mean
125 income days, respectively. At present, the majority (92%) of patients with GBS in Bangladesh
126 receive supportive care only.¹⁴ In addition, mobile PE equipment is not available in Bangladesh;
127 therefore, patients admitted to the intensive care unit (ICU) cannot receive PE. We previously
128 reported the mortality rates for GBS in Bangladesh range from 12 to 14% and observed 29% of
129 patients with GBS in Bangladesh are unable to walk at 6 months after onset; these poor outcomes
130 are undoubtedly due to the low rates of specific treatment with PE or IVIg.^{15 16}

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3 132 Small volume plasma exchange (SVPE) may represent a cheap, effective alternative treatment for
4
5 133 GBS. SVPE is based on the same principle as conventional PE (selective removal of plasma) but
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7 134 uses a novel, simple technique with much lower costs (approximately 500 US\$). The current non-
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9 135 randomized trial was designed to investigate the safety and feasibility of SVPE in 20 patients
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11 136 with GBS admitted to the National Institute of Neurosciences Hospital in Dhaka, Bangladesh.

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15 138 **Methods/Design**

16 139 *Study design*

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20 140 For this non-randomized, single arm, interventional safety and feasibility trial, 20 adult patients
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22 141 with GBS were enrolled between March 2016 and December 2016 for SVPE at the National
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24 142 Institute of Neurosciences and Hospital (NINS), Dhaka, Bangladesh. A detailed study protocol
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26 143 was published previously and includes definitions of all variables used in this study.¹⁷

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31 145 Four to six daily sessions of whole blood sedimentation and removal of supernatant plasma after
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33 146 re-transfusion of the sedimented blood cells was planned for the 20 patients with GBS, with a
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35 147 target of removing an overall volume of at least 8 litres (L) of plasma over a total of 8 days.¹⁷
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37 148 (See supplementary video for SVPE procedure)

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42 150 Patients with GBS were monitored according to a standard protocol throughout the course of
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44 151 SVPE until the second day after withdrawal of the central venous catheter (CVC) in order to
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46 152 assess predefined measures of safety and feasibility and followed up for six months to assess
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48 153 neurological outcome. The protocol was reviewed and approved by the institutional research and
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50 154 ethics review committees at the icddr,b and registered at clinicaltrials.gov (NCT02780570).¹⁷ All
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52 155 patients provided written informed consent to participate in this study.

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3 157 *Patient and Public Involvement*
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5 158 Patients and or public were not involved either in the development of the research question, study
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7 159 design and outcome measure or recruitment to and conduct of the study.
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11 161 *Inclusion and exclusion criteria for patients with GBS*
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13 162 Patients aged ≥ 18 -years-old fulfilling the diagnostic criteria for GBS of the National Institute of
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15 163 Neurological and Communicative Disorders and Stroke (NINDS)¹⁸ were enrolled, provided they
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17 164 were unable to walk unaided for more than 10 meters (GBS disability score ≥ 3), presented
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19 165 within 2 weeks of the onset of weakness, and were unable to afford standard treatment with IVIg
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21 166 or PE. Patients with concomitant severe or terminal illnesses, evidence of healthcare-associated
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23 167 infection (HAI) on admission (except for aspiration pneumonia), a previous history of severe
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25 168 allergic reactions to properly matched blood products, and pregnant women were excluded from
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27 169 the study.
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33 171 *Control cohort*
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35 172 To compare the safety of SVPE in patients with GBS in the context of the background risk of
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37 173 central line-associated blood stream infection (CLABSI) at our institution, we prospectively
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39 174 assessed the incidence of CLABSI in a hospital control group of 24 adult patients without GBS
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41 175 receiving neurocritical care. Hospital controls were eligible based on the following
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43 176 characteristics: ≥ 18 -years-old, a neurological diagnosis other than GBS, and a CVC placed for $>$
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45 177 2 and ≤ 8 calendar days after admission to the same ICU or HDU unit as the SVPE-treated
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47 178 patients. Patients with a HAI (except aspiration pneumonia) and pregnant women were excluded
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49 179 from the control group.
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3 182 *Primary and secondary outcome measures*

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5 183 The primary outcome measures of safety were the number of patients with GBS treated with
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7 184 SVPE who developed either severe sepsis or septic shock due to CLABSI¹⁹ and the occurrence of
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9 185 venous thrombosis in the limb where the CVC was placed. The primary outcome measure of
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11 186 feasibility was the ability to remove at least 8 L of plasma over 8 days.

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13 187 The secondary outcome measures of the safety of SVPE were the relative risk of CLABSI due to
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15 188 SVPE (compared to CLABSI in the hospital control group without GBS), hemodynamic
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17 189 instability during the SVPE procedure, and development of anaemia (Hb < 8 gm/dL) or any
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19 190 catheter-related haemorrhage requiring a blood transfusion.

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22 191 The secondary outcome measure of feasibility of SVPE was the rate of CVC occlusion during the
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24 192 SVPE procedure. In addition, neurological outcome was assessed using the GBS disability
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26 193 score²⁰, MRC sum score²¹, Overall Neuropathy Limitation Scale (ONLS)²² and Rasch-built
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28 194 Overall Disability Scale (R-ODS)²³ at 1st, 2nd, 3rd, and 6th months from the start of SVPE.

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33 196 *Procedure safety and documentation*

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35 197 Strict aseptic procedures were followed to prevent CLABSI.²⁴⁻²⁶ SVPE was documented in terms
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37 198 of the duration and amount of plasma removed in each session, and the type and volume of
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39 199 replacement fluid and fresh frozen plasma (FFP) used. Throughout the procedure, the
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41 200 haemodynamic, haematological, biochemical, coagulation and infection profiles of the SVPE-
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43 201 treated patients were monitored according to the protocol.¹⁷ Screening for hepatitis B and C
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45 202 viruses, human immunodeficiency virus (HIV) and syphilis were performed as patient baseline
46
47 203 assessments, and also on donor FFP before administration. CLABSI, primary and secondary
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49 204 bloodstream infections¹⁹, catheter-associated urinary tract infection (CAUTI)²⁷, ventilator-
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51 205 associated pneumonia (VAP)²⁸ and other HAI^{29 30} were documented in the SVPE-treated patients
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53 206 with GBS and the hospital control group.

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3 207 *Sample size*

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5 208 This safety and feasibility study enrolled 20 patients with GBS for SVPE. We could not
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7 209 perform a formal power calculation for this safety and feasibility study. The sample size
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9 210 was based on previous pilot studies conducted in GBS.^{31 32} The baseline rate of CLABSI
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11 211 was measured in the hospital control group of 24 patients without GBS admitted to the
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13 212 same study facility who required a CVC for at least 8 days during the study period.
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18 214 *Stopping rules for the trial based on safety and feasibility*

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20 215 Decision to stop the SVPE trial was designated using a Bayesian approach.³³⁻³⁵
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22 216 Accordingly, a predictive success rate of 75% was predefined for the SVPE procedure. If
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24 217 more than 5 of 20 patients experienced an SAE, or if it appeared impossible to remove at
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26 218 least 8 L of plasma over 8 days in at least 15 of 20 patients, the procedure was considered
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28 219 unsafe or unfeasible.
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33 221 *Statistical analysis*

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35 222 The rate of HAIs (CLABSI, VAP and CAUTI) per 1000 device days were calculated by
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37 223 dividing the number of each HAI during the study period by the number of device days and
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39 224 multiplying the result by 1000. The infection safety profile for SVPE was assessed by
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41 225 calculating the standardized infection ratio to define the risk of HAIs in patients with GBS
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43 226 treated with SVPE. The standardised infection ratio (SIR) was calculated by dividing the
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45 227 number of observed HAI by the number of HAI predicted (i.e., the infection rate in the control
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47 228 group). The predicted HAI rate was calculated using the rates of HAI in the hospital control
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49 229 group of patients without GBS during the study period. Percentage values were compared using
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51 230 the Chi-square test or Fisher's exact test (two-tailed) and median values, the Mann-Whitney U-
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53 231 test using SPSS 22 software (IBM SPSS Statistics for Windows Version 22.0., IBM Corp.,
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3 232 Armonk, NY, USA). Analyses were performed on an intention-to treat basis. All *P*-values
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5 233 reported are two-sided; $p < 0.05$ was considered significant.
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9 235 **Results**

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11 236 *Patients and hospital controls*

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13 237 The demographic and clinical characteristics of the 20 patients with GBS are given in Table 1.

14
15 238 The median age of the patients with GBS was 33 years (range; 18-55); median body weight was
16
17 239 60 kg (IQR, 55-65 kg; range, 50-72 kg) and 13 (65%) patients were male (Fig. 1). On admission
18
19 240 and before the start of SVPE, all 20 patients with GBS were unable to walk independently (GBS
20
21 241 disability score, 4). One patient required mechanical ventilation from the second day after the
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23 242 onset of weakness; SVPE was started on the fourth day of mechanical ventilation (patient 9, Fig.
24
25 243 1). Two of the 19 patients who did not require mechanical ventilation at the start of the study
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27 244 required mechanical ventilation on the second day after initiation of SVPE (patients 11 and 19,
28
29 245 11 and 2 days after the onset of weakness, respectively; Fig. 1). The median MRC sum score for
30
31 246 the limb muscles in all 20 patients was 20 (IQR: 0-29; range: 0-36; Fig. 1). Symptoms of a
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33 247 preceding infection in the 4 weeks before the onset of weakness were present in 18 (90%)
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35 248 patients with GBS, of whom 10 (50%) had diarrhoea. Median duration from admission to start of
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37 249 SVPE was two days (IQR, 2-3 days; range, 0-7 days). Median duration to nadir from the onset of
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39 250 weakness was five days (range, 1-13 days). Electrodiagnostic nerve conduction studies indicated
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41 251 15 (75%) patients had an axonal subtype and 5 (25%) patients had a demyelinating subtype of
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43 252 GBS. Median duration from onset of weakness to NCS examination was 10 days (range, 4-16
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45 253 days). All patients had albuminocytologic dissociation; median CSF protein was 166 mg/dL
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47 254 (range 117-253 mg/dL). Median duration from onset of weakness to CSF examination was 11
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49 255 days (range, 4-17 days).
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3 257 Median age of the 24 hospital control patients without GBS was 44 years (IQR, 25-57; range; 18-
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5 258 74); 10 (42%) were male. Age and gender distribution were not significantly different compared
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7 259 to the 20 patients with GBS ($p = 0.2155$, $p = 0.1434$, respectively). The diagnoses for these 24
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9 260 patients were: brain tumour ($n = 5$), transverse myelitis ($n = 5$), head trauma after road traffic
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11 261 accident ($n = 3$), viral meningoencephalitis ($n = 2$), myasthenia gravis ($n = 2$), compressive
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13 262 cervical myelopathy ($n = 2$), cerebrovascular accident ($n = 2$), motor neuron disease ($n = 1$),
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15 263 electrolyte imbalance ($n = 1$) and status epilepticus ($n = 1$).
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20 265 *Primary endpoints*

21
22 266 One patient with GBS treated with SVPE developed severe sepsis, possibly due to SVPE-related
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24 267 CLABSI (SVPE window-period blood culture revealed methicillin-resistant *Staphylococcus*
25
26 268 *aureus*). This patient required intravenous fluid, noradrenalin infusion and intravenous
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28 269 antibiotics, but eventually improved (patient 11, Fig. 1). This patient also had signs and
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30 270 symptoms suggestive of aspiration pneumonia and VAP; *Streptococcus spp.* was isolated from
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32 271 pulmonary aspirates. Further laboratory results revealed dys-electrolytemia, anaemia and hypo-
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34 272 albuminemia. No patients experienced deep vein thrombosis due to the CVC for SVPE. Fifteen
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36 273 (75%) of the 20 patients met the primary endpoint of feasibility, defined as the ability to remove
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38 274 at least 8 L of plasma in eight days. The median volume of plasma removed was 8.5 L (IQR, 7.9-
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40 275 8.8 L; range, 6.3-9.6 L; Fig. 1). The median plasma exchange rate was 140 mL/kg bodyweight
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42 276 (IQR, 125-155 mL/kg; range, 110-175 mL/kg) over 8 days and 16 (80%) patients had a plasma
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44 277 exchange rate > 120 mL/kg (Table 2).
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3 282 *Secondary endpoints*

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5 283 *Infections among SVPE-treated patients with GBS and hospital controls*

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7 284 Among the 20 patients with GBS treated with SVPE, six (30%) had fever during SVPE (Fig. 1,
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9 285 Supplementary Figure 1), including 2 (10%) patients with leucocytosis who were diagnosed with
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11 286 HAI (VAP and CAUTI in one patient; VAP in one patient). In three out of four (20%) patients
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13 287 with fever without leucocytosis, fever subsided within two to three days without antimicrobial
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15 288 therapy (Fig. 1). The remaining patient with pyrexia without leucocytosis had microbiological
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17 289 evidence of both CLABSI and VAP (patient 11, Fig. 1). In all other 14 patients with GBS, no
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19 290 fever was documented during the course of SVPE until the tenth day of SVPE (second day after
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21 291 removal of the CVC for SVPE). Five of these 14 patients had leucocytosis, but no site-specific
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23 292 HAI could be detected. However, one of the nine patients without fever but leucocytosis fulfilled
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25 293 the criteria for CAUTI (patient 12, Fig. 1). All three patients who required mechanical ventilation
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27 294 subsequently developed VAP; two of the 13 patients who required a urinary catheter developed a
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29 295 CAUTI (patient 11, Fig. 1). No patients died during the 6 months follow-up.

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35 297 All 24-hospital control patients without GBS required mechanical ventilation and an indwelling
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37 298 urinary catheter. Of these patients, 22 (92%) patients had fever, of whom 15 (63%) had
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39 299 leucocytosis; a diagnosis of a specific HAI could be made 14 of these 15 patients (CLABSI in
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41 300 two, CAUTI in one, VAP in 11) and four (17%) fulfilled the criteria for severe sepsis
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43 301 (Supplementary Figure 1). Seven (29%) of the 24 hospital control patients had fever without
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45 302 leucocytosis. In two of these seven patients, a specific HAI was diagnosed (CAUTI and VAP in
46
47 303 one, and VAP in one). In two hospital control patients, no fever was documented until day 10
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49 304 after first placement of the CVC, but leucocytosis was present and no site-specific HAI could be
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51 305 detected (Supplementary Figure 1).

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3 307 The rates of CLABSI, CAUTI and VAP per 1000 device days in the SVPE-treated patients with
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5 308 GBS were 6.25, 19.2 and 40 compared to 10.4, 10.4 and 67.7 for the hospital control patients
6
7 309 without GBS, respectively. The relative risks of CLABSI, CAUTI and VAP associated with
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9 310 SVPE were 0.6, 1.2 and 1.8, respectively, compared to hospital control patients. The rates of
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11 311 CLABSI, CAUTI and VAP were comparable between SVPE-treated patients with GBS and
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13 312 hospital control patients ($p > 0.05$). Antimicrobial agents were used more frequently in the
14
15 313 hospital control patients ($p < 0.0001$; Fig. 2). The standardised infection ratios for CLABSI,
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17 314 CAUTI and VAP for SVPE-treated patients with GBS were 0.6, 1.8 and 1.9, respectively.
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22 316 *Other secondary endpoints*

23
24 317 Ten (50%) of the 20 patients treated with SVPE experienced transient hypotension during SVPE,
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26 318 which was corrected by infusion of 200-300 mL crystalloid saline (Fig. 1). Minor bleeding
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28 319 through the CVC insertion site (excluding at the time of insertion) was observed in 10/20 patients
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30 320 (50%; Fig. 1); these bleeds required a pressure pack. Reduction of the anticoagulant dose along
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32 321 with a pressure pack was required in 3/20 patients, who all had a prolonged prothrombin time
33
34 322 (PT). Three patients had single episode of haemorrhage through the urinary catheter: one was
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36 323 diagnosed with a CAUTI with normal coagulation profile, one had a prolonged PT, the other had
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38 324 sterile haematuria with normal PT. Overall, PT and activated partial thromboplastin time (aPTT)
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40 325 were prolonged in 4/20 patients and only PT was prolonged in 2/20 patients. Clotting time and
41
42 326 bleeding time were not prolonged in any patient. One patient developed anaemia (haemoglobin, 8
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44 327 gm/L) at the end of SVPE; this patient also had severe sepsis and required one unit of blood
45
46 328 transfusion (patient 11, Fig. 1). CVC blockages were not observed in any SVPE-treated patients
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48 329 with GBS. One patient with increased clotting tendency who required an increased dose of low
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50 330 molecular weight heparin had shortened clotting time (CT) ($< 50\%$ of upper limit of normal),
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52 331 though PT was normal (patient 10, Fig. 1).
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3 332 The neurological outcomes of the SVPE-treated patients with GBS at six months in terms of
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5 333 neurological scores are given in Table 3. Median time to recover the ability to walk unaided was
6
7 334 4 weeks (Fig. 3). Fourteen (70%) of the 20 patients had an improvement in GBS disability score
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9 335 of one or more grades at four weeks after the onset of SVPE. At one month, 12 patients (60%)
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11 336 were able to walk unaided, two patients (10%) were able to walk aided and six (30%) patients
12
13 337 were bedbound, of whom three still required mechanical ventilation. At three months, 14 (70%)
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15 338 patients were able to walk unaided, one (5%) could walk with aid and five (25%) patients were
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17 339 bedbound. At six months, 14 (70%) patients were able to walk unaided, three (5%) could walk
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19 340 with aid and three (15%) remained bedbound (Table 3).
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24 342 *Other relevant clinical and laboratory findings*

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26
27 343 Allergic/transfusion reaction to FFP was observed in four patients with GBS treated with SVPE
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29 344 (Fig. 1). These transfusion reactions presented as an itchy erythematous skin rash (three patients),
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31 345 fever (two patients), hypotension (one patient) following transfusion of FFP; all of these reactions
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33 346 were managed with oral antihistamine (and intravenous saline in one patient) without further
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35 347 complications.
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40 349 The other documented haematological and biochemical abnormalities were hypo-albuminemia (n
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42 350 = 4), thrombocytopenia ($n = 6$), hyponatraemia ($n = 1$), hypokalaemia ($n = 3$), hypomagnesaemia
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44 351 ($n = 1$), hypocalcaemia ($n = 3$); (Table 2).
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48 353 *Immunoglobulin dosage admitted by FFP*

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51 354 During SVPE the median volume of FFP received per GBS patient as replacement fluid was
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53 355 6000 ml (range, 5000 ml to 6000 ml). Considering the normal plasma IgG level of 11.20 mg/ml
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3 356 (range, 6.9 mg – 17.6 mg)³⁶, SVPE treated GBS patients received IgG dose of median 0.9 g/kg
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5 357 (range 0.6 g/kg – 1.3 g/kg).
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7 358

9 359 **Discussion**

11 360 *Principal findings*

13 361 This study suggests SVPE may represent a safe and feasible alternative to conventional plasma
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15 362 exchange for patients with severe GBS in limited-resource settings. Of the 20 patients in this
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17 363 study, one (5%) experienced a SAE (severe sepsis due to probable CLABSI). The rate of SAE
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19 364 was not significantly higher than the hospital control group without GBS with a CVC, and no
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21 365 patients had a CVC-related thromboembolic event in patients with SVPE. We were able to
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23 366 remove the prespecified target volume (8 L) of plasma as the target primary endpoint of
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25 367 feasibility in 15/20 (75%) patients with GBS. Median plasma exchange volume and rate during
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27 368 SVPE were 8.4 L and 140 mL/kg, respectively. Minor adverse effects included transient
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29 369 hypotension during SVPE in 50% (10/20), minor haemorrhage from CVC insertion site in 50%
30
31 370 (10/20), transfusion reaction to fresh frozen plasma in 20% (4/20), and hypo-albuminemia,
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33 371 anaemia and electrolyte imbalance in 20% (4/20) of patients. An improvement of at least one
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35 372 grade on the GBS disability score was observed for 14/20 (70%) patients at four weeks after the
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37 373 initiation of SVPE. No patients died.
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44 375 *Comparison with baseline hospital control patients and standard/modified PE*

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46 376 With respect to HAIs, no significant differences were observed in the frequency of CLABSI,
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48 377 severe sepsis, VAP or CAUTI between the SVPE-treated patients with GBS and 24 hospital
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50 378 control patients without GBS treated using a CVC in the same ICU or HDU (Fig. 2). However,
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52 379 antimicrobial agents were used more frequently, usually prophylactically, in the hospital control
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54 380 patients compared to the patients with GBS treated with SVPE ($p < 0.0001$; Fig. 2). The
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3 381 probability of detecting microorganisms in clinical infections may have been reduced due to
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5 382 overzealous use of antibiotics in the hospital control patients. Early trials of PE in patients with
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7 383 GBS showed 34% of patients develop severe infections.^{7 11} Subsequently, another large trial
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9 384 documented septicaemia in 19% of patients.⁵ However, the rates of CLABSI were not reported.
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11 385 The volume exchanged during SVPE is within the range recommended as per one large RCT on
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13 386 PE [120-200 mL/kg (standard PE)⁷ vs. 140 mL/kg for SVPE]. In GBS exchange of 6 L of plasma
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15 387 in adult patients is clinically beneficial in mild to moderate cases and less effective than exchange
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17 388 of 12 L in severe cases, however exchanging 18 L provides no added benefit over 12 L in severe
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19 389 cases of GBS.⁵ This suggests that the correlation between clinical benefit and the volume of
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21 390 plasma removed is not linear and exchanging more than 6 L of plasma is likely to have a
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23 391 beneficial effect. During the piloting of the SVPE procedure we assessed that removal of 1 L of
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25 392 patient plasma could be feasible in a day. Therefore we defined our target plasma volume of 8 L
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27 393 to be removed in 8 days. We were able to remove >120 mL/kg plasma in 80% of patients, which
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29 394 should provide a therapeutic effect.³⁷ Notably, the body weight of our patients may be lower than
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31 395 that of patients in western countries. In addition, SVPE was complete within 8 days, shorter than
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33 396 the usual time required for a full session of PE (10 to 14 days).
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39 398 Replacement fluid used in SVPE was FFP. We have several justifications in favour of using FFP
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41 399 instead of human albumin or other available colloidal solutions available in Bangladesh. First
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43 400 FFP is safe in terms of microbiological safety since stringent screening for viral and bacterial
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45 401 contamination was performed before infusion. Second, in contrast to human albumin and colloid
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47 402 solutions, FFP contains normal human IgG that could contribute beneficial immunotherapeutic
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49 403 effect in GBS and previously used as replacement fluid in large PE trials.^{4 5} SVPE treated GBS
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51 404 patients received approximately half the amount of IgG from the FFP used as replacement fluid
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53 405 compared to the total IVIg doses traditionally used in GBS (2gm/kg). Third, FFP contains all
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3 406 human plasma proteins that helps preservation of plasma colloid osmotic pressure and prevents
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5 407 formation of oedema and hypotension. Lastly FFP is much cheaper than commercial human
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7 408 albumin.

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11 410 In each day three units of FFP were transfused as replacement fluid after the last session of SVPE
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13 411 and in the initial two to three sessions, normal saline was used as replacement fluid. This was
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15 412 done to achieve the maximum immunotherapeutic effect of FFP as SVPE was not resumed before
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17 413 the next day and the IgG in FFP remained in the circulation overnight for a longer period of time
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19 414 (10 to 12 hours). However due to long half life of IgG this effect may have reduced due to
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21 415 repeated plasma removal between the transfusion of FFP throughout the course of SVPE.
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26 417 In GBS, treatment with modified methods of PE done previously, were device based and done on
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28 418 limited number of GBS patients. In one study on 25 GBS patients from India, daily removal of
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30 419 small volume of plasma (10-15 ml plasma/kg body weight) for duration of median 3 days using
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32 420 traditional PE machine was shown to be clinically beneficial.³⁸ In another study from the same
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34 421 country, 12 GBS patients were treated with PE over 10 days using different PE-machine kit
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36 422 (REF627 kit from Haemonetics Corporation Limited on MCS+ machine) where authors claimed
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38 423 clinical improvement, however the main focus was on cost effectiveness and the total plasma
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40 424 volume exchanged per patient was not mentioned.³⁹ Nevertheless these methods are based on
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42 425 specific devices those are not in common practice, nor the trained personnel for these are
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44 426 available in the developing countries.
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50 428 Important observations in terms of secondary endpoints were transient hypotension, transfusion
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52 429 reaction to FFP and minor bleeding through the CVC insertion site. Hypotension is a common
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54 430 complication during traditional PE that affects nearly half of patients.⁵ Spells of hypotension
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3 431 during SVPE were more frequent during the three to four days after initiation of SVPE, and could
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5 432 be easily corrected by rapid infusion of 300-400 mL saline (Fig. 1). The hypotension could
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7 433 possibly be explained by hypovolemia due to drawing blood or as a result of the compromised
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9 434 autonomic nervous system in patients with GBS. As SVPE proceeded, hypotensive spells were
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11 435 encountered less frequently despite drawing the same volume of blood, which may in part be
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13 436 explained by adaptation of the vasomotor system or recovery from autonomic dysfunction. Minor
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15 437 bleeding through the CVC insertion site occurred in 50% of patients and could be controlled by
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17 438 applying a simple pressure pack over the CVC insertion site in most cases; mild prolonged PT
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19 439 was noted in 30% (3/10) patients. However, spontaneous bleeding usually occurs if the PT is
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21 440 more than 2.5 times prolonged and PC is < 0.50 lac/ μ L.⁴⁰ Movement of the limb where the CVC
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23 441 was placed may have caused traction on the CVC and contributed to local bleeding in the other
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25 442 seven patients. Haematuria is not uncommon in patients with a UTI, as may have occurred in one
26
27 443 SVPE treated patient; traumatic traction of the urinary catheter may cause haematuria in two
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29 444 other catheterized SVPE-treated patient taking oral aspirin, who had haematuria and sterile urine.
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31 445 We also monitored the major organ function and biochemical status of the patients treated with
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33 446 SVPE. No patients experienced hepatic or renal impairment. One patient developed anaemia and
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35 447 hypoalbuminemia; this patient had severe sepsis, a common cause of anaemia and
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37 448 hypoalbuminemia in critically ill patients admitted to an ICU (patient 11, Fig. 1). Electrolyte
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39 449 imbalances were detected in 15% of the SVPE-treated patients with GBS, and were mild,
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41 450 subclinical and easily corrected.
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48 452 The median reported durations to recovery of independent walking in patients with GBS in large-
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50 453 scale RCTs after PE are 53, 52 and 70 days^{4 5 7}; compared to 30 days in our patients treated with
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52 454 SVPE. Moreover, 60% of the patients with GBS treated with SVPE were able to walk
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54 455 independently at four weeks, whereas 20% of patients with GBS acquired independent walking
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3 456 ability at four weeks after traditional PE. However, these differences may possibly be due to the
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5 457 small sample size and variations in demographic and neurophysiological characteristics between
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7 458 cohorts. Finally, SVPE was completed in all 20 patients and no patients died.
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10 11 460 *Limitations of SVPE*

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13 461 SVPE is a time-consuming and labour-intensive procedure, which is a limitation. We used
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15 462 multiple thin-lumen tubing systems interconnected with a multichannel connector device, which
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17 463 may increase the chance of blood coagulating within the tubing system. Coagulation may require
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19 464 manipulation or replacement of the tubing to ensure free flow of blood and saline. Such handling
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21 465 could increase the chance of microbial contamination. A single continuous wide-lumen tubing
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23 466 system (SVPE kit) could resolve this problem. Most importantly, personnel conducting the SVPE
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25 467 procedure should maintain proper aseptic technique, which can sometimes be challenging in
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27 468 developing countries. Furthermore, other adaptations such as provision of a larger blood bag or
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29 469 increasing the number of days for SVPE could be considered to increase the plasma exchange
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31 470 rate.
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36 37 472 *Clinical implications and future research*

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39 473 Despite the limitations, our study showed SVPE is a safe and feasible treatment for GBS in a
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41 474 resource-limited setting where IVIg or PE are either unavailable or unaffordable. Specifically, the
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43 475 poorest 20% of the world's population (1.8 billion people) who typically earn less than 10 US\$
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45 476 per day and who are not covered by a national health insurance system may benefit. Considering
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47 477 the incidence of GBS is 2/100,000 in developing countries, approximately 40,000 patients could
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49 478 potentially benefit from SVPE every year, worldwide. In the future, a multicentre RCT is
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51 479 required to assess the clinical efficacy of SVPE for patients with GBS. If proven effective, SVPE
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53 480 could be an affordable and easily available alternative plasma exchange technique in low-income
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3 481 countries for patients with GBS and other disorders, who at present cannot afford standard PE
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5 482 due to its high cost and unavailability.

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10 484 **Declarations**

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12
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33
34 494 size of the study. MV, MVJ, SR, and HPE contributed to the infection safety guidelines in the
35
36 495 study design. BI and QDM conducted the study and BI collected and analysed the data and
37
38 496 drafted the manuscript. All authors have critically revised the manuscript and have read and
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40 497 approved the final manuscript.
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4
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13
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20
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22
23 512 reviewed and approved this study protocol on 09/12/2015 (reference number: PR-15086, version
24
25 513 no 3).
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29 515 *Patient consent:* Obtained.
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34 517 *Data sharing:* The dataset is available from the lead author on request.
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36 518

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38 519 *Transparency:* The corresponding author affirms that the manuscript is an honest, accurate and
39
40 520 transparent account of the study being reported; that no important aspects of the study have been
41
42 521 omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have
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44 522 been explained.
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661 Table 1: Demographic and clinical characteristics of the 20 patients with GBS included in this
 662 small volume plasma exchange (SVPE) study at entry
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Characteristic	Value
Demography	
Sex [males: females (ratio)]	13:7 (1.85)
Age (years) ¶	33 (18 - 55)
Body weight (kg) ¶	60 (50 - 72)
Antecedent events ‡ (total)	18 (90%)
Diarrhoea	10 (50%)
Respiratory infection	5 (25%)
Fever	3 (15%)
Days from antecedent events to weakness ¶	7 (3 - 30)
Days between onset of weakness to admission ¶	7 (2-12)
Neurological deficits at entry	
Weakness in arms and legs	20 (100%)
Cranial nerve deficits	12 (60%)
Decreased deep tendon reflexes	20 (100%)
Sensory involvement	5 (25%)
GBS disability score §	4 19 (95%)
	5 1 (5 %)
Severity of weakness (MRC sum-score) ¶	20 (0-29)
Autonomic dysfunction	11 (55%)

664 ¶ Median (range); † increased protein level (> 45 mg/dL) in combination with CSF cell count <
 665 50/µL; CSF = cerebrospinal fluid; NCS = nerve conduction study; ‡ symptoms of an infection in
 666 the four weeks preceding the onset of weakness; § GBS disability score (0 - 6) = 0: healthy state;
 667 1: minor symptoms and capable of running; 2: able to walk 10 meters or more without assistance
 668 but unable to run; 3: able to walk 10 meters across an open space with help; 4: bedridden or
 669 chair-bound; 5: requiring assisted ventilation for at least part of the day; 6: dead.

670 Table 2: Treatment characteristics and complications associated with SVPE in the 20 patients
671 with GBS

Characteristic/complication	Value
Treatment characteristics	
Number of sessions of SVPE per patient [¶]	30 (24 - 42)
Volume of plasma removed per patient [¶]	8.4 (6.3 – 9.6)
Plasma exchange rate (mL/kg) [¶]	140 (110-175)
Time between hospital admission and SVPE (days) [¶]	8 (5-10)
Time between onset of weakness and start of SVPE (days) [¶]	8 (5-10)
Need to stop SVPE due to poor hemodynamic tolerance	0/20 (0%)
Need for blood transfusion for anaemia	1/20 (5%)
Reduction of anticoagulant drug dose for bleeding	3/20 (15%)
Temporary withdrawal of antiplatelet drug for bleeding	4/20 (20%)
Increased anticoagulant drug dose to continue SVPE	1/20 (5%)
CVC blockade/replacement	0/20 (0%)
Complications during SVPE	
<i>Infection</i>	
Leukocytosis	7/20 (35%)
CLABSI [§]	6.25
VAP [§]	136.4
CAUTI [§]	40
Severe sepsis	1/20 (5%)
Antimicrobial agents used	6/20 (30%)
<i>Bleeding and coagulation</i>	
Bleeding from CVC insertion site	10/20 (50%)
Bleeding from mucosal area	3/20 (15%)
Prolonged BT (BT > 10 min)	0/20 (0%)
Prolonged CT (CT > 15 min)	0/20 (0%)
Prolonged PT (PT > 14 sec) [¶]	6/20 (30%) [15-19 sec]

Prolonged aPTT (aPTT > 40 sec) ¶	3/20 (15%) [51-240 sec]
<i>Other complications</i>	
Saline responsive hypotension	10/20 (50%)
Anaemia (Hb < 8 gm/L)	2/20 (10%)
Thrombocytopenia (PC < 1.5 lac/µL) ¶	6/20 (30%) [0.79-1.3 lac/µL]
Jaundice (serum bilirubin > 1.2 mg/dL)	0/20 (0%)
Renal impairment (serum creatinin > 1.2 mg/dL)	0/20 (0%)
Hyponatraemia (serum Na ⁺ < 135 mEq/L)	1/20 (5%) [126 mEq/L]
Hypokalaemia (serum K ⁺ < 3.5 mEq/L) ¶	3/20 (15%) [2.6-3.2 mEq/L]
Hypoalbuminemia (serum albumin > 35 gm/L) ¶	4/20 (20%) [26-32 gm/L]
Hypocalcaemia (serum Ca ⁺ < 2.2 mmol/L) ¶	3/20 (15%) [1.89-1.98 mmol/L]
Hypomagnesaemia (serum Mg ⁺ < 75 mEq/L) ¶	1/20 (5%) [73 mEq/L]
Hypersensitivity/transfusion reaction to FFP	4/20 (20%)

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673 ¶ Median (range); § rate per 1000 device days; CLABSI: central line-associated bloodstream
674 infection; VAP: ventilator-associated pneumonia; CAUTI: catheter-associated urinary tract
675 infection; CVC: central venous catheter; BT: bleeding time, CT: clotting time; PT: prothrombin
676 time; APTT: activated partial thromboplastin time; FFP: fresh frozen plasma.

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678 Table 3: Neurological outcomes of the 20 patients with GBS after SVPE
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Clinical outcome	1 month	2 months	3 months	6 months
Cranial nerve involvement	7/20 (35%)	6/20 (30%)	4/20 (20%)	2/20 (10%)
Autonomic involvement	3/20 (15%)	3/20 (15%)	0/20 (0%)	0/20 (0%)
Sensory dysfunction	1/20 (5%)	1/20 (5%)	1/20 (5%)	1/20 (5%)
GBS disability score [¶]	0 = 0	0 = 1	0 = 1	0 = 2
	1 = 3	1 = 6	1 = 7	1 = 7
	2 = 9	2 = 6	2 = 6	2 = 5
	3 = 2	3 = 1	3 = 1	3 = 3
	4 = 3	4 = 5	4 = 5	4 = 3
	5 = 3	5 = 1	5 = 0	5 = 0
MRC sum score [†] *	47 (0-60)	49 (0-60)	53 (6-60)	58 (22-60)
ONLS [‡] *	4 (1-12)	3 (0-12)	3 (0-12)	2 (0-10)
R-ODS [§] *	26 (0-41)	33 (0-45)	37 (0-45)	38 (0-46)

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681 * Median (range); ¶ GBS disability score (0 - 6) = 0: healthy state, 1: minor symptoms and
682 capable of running, 2: able to walk 10 meters or more without assistance but unable to run, 3:
683 able to walk 10 meters across an open space with help, 4: bedridden or chair-bound, 5: requiring
684 assisted ventilation for at least part of the day, 6: dead; † MRC sum score: Medical Research
685 Council sum score; ‡ ONLS: Overall Neuropathy Limitation Scale²²; § R-ODS: Rash-built
686 Overall Disability Score²³

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3 697 **Figure 1:** Feasibility of SVPE and associated complications for the 20 individual patients with
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9 700 SVPE: small volume plasma exchange, HAI: hospital acquired infection, V: ventilator-associated
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11 701 pneumonia, B: central line-associated blood stream infection, U: catheter-associated urinary tract
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13 702 infection, ^A measured in litres, ●: spell of hypotension (systolic BP < 90 mm Hg), ◊ : CVC
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15 703 insertion site bleeding, ▲: hypersensitivity to fresh frozen plasma, shaded squares: pyrexia due to
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17 704 bacterial infection, dotted squares: pyrexia due to suspected viral infection, M: onset of mechanical
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19 705 ventilation, C: urinary catheterization.

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27 708 **Figure 2:** Hospital-acquired infections and use of antibiotics in the 20 patients with GBS receiving
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29 709 SVPE compared to the 24 hospital control patients without GBS treated in an ICU with a CVC who
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31 710 did not receive SVPE.

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34 712 ■ SVPE ($n = 20$): twenty patients with GBS aged ≥ 18 -years-old who were bedbound (GBS
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36 713 disability score ≥ 4) received small volume plasma exchange (SVPE) within 2 weeks of the onset
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38 714 of weakness. □ Non-SVPE ($n=20$): twenty-four patients aged ≥ 18 -years-old with a diagnosis
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40 715 other than GBS who required a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU
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42 716 and HDU units in the same period as the patients with GBS received SVPE; * $p < 0.0001$.

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50 719 **Figure 3:** Kaplan-Meier estimate (with 95% confidence limits) of the cumulative incidence of
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52 720 restoration of independent walking ability in patients with GBS treated with SVPE.

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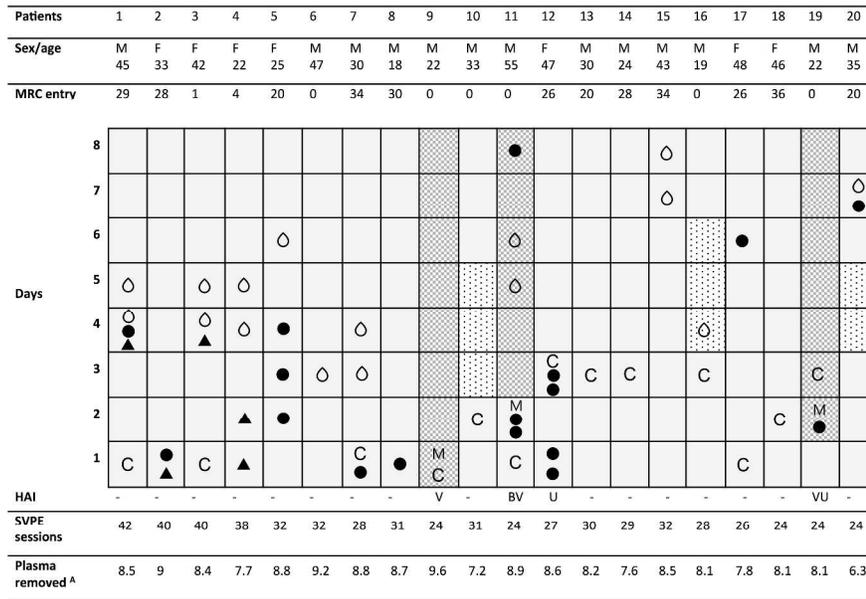


Figure 1: Feasibility of SVPE and associated complications for the 20 individual patients with GBS. SVPE: small volume plasma exchange, HAI: hospital acquired infection, V: ventilator-associated pneumonia, B: central line-associated blood stream infection, U: catheter-associated urinary tract infection, A measured in litres, black dot: spell of hypotension (systolic BP < 90 mm Hg), empty drop: CVC insertion site bleeding, black triangle: hypersensitivity to fresh frozen plasma, shaded squares: pyrexia due to bacterial infection, dotted squares: pyrexia due to suspected viral infection, M: onset of mechanical ventilation, C: urinary catheterization.

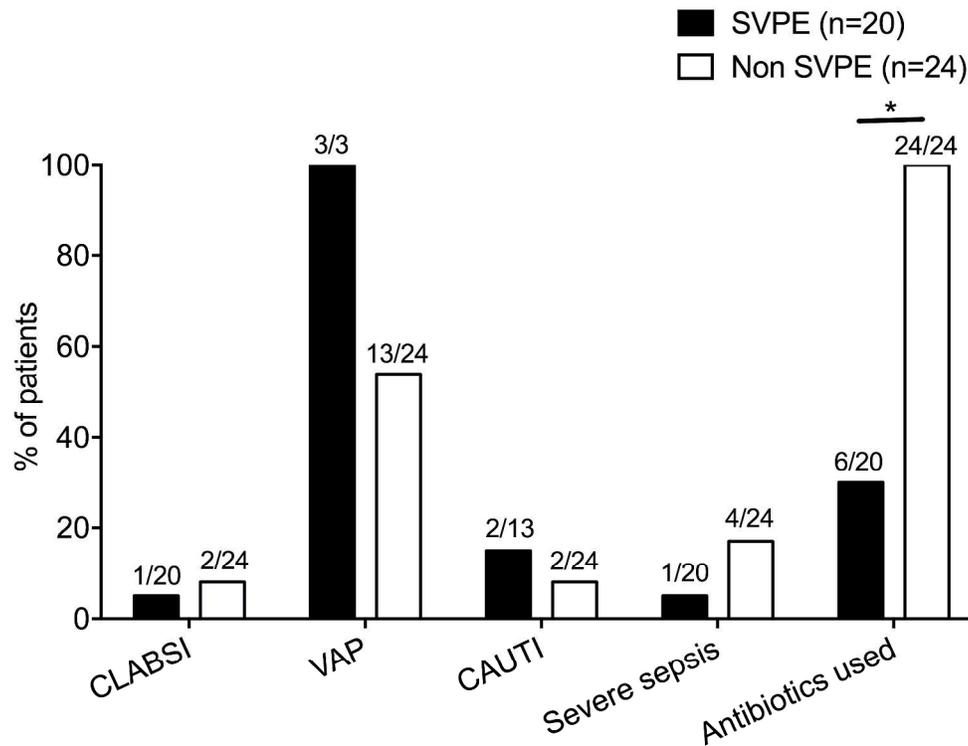


Figure 2: Hospital-acquired infections and use of antibiotics in the 20 patients with GBS receiving SVPE compared to the 24 hospital control patients without GBS treated in an ICU with a CVC who did not receive SVPE.

■ SVPE (n = 20): twenty patients with GBS aged ≥ 18 -years-old who were bedbound (GBS disability score ≥ 4) received small volume plasma exchange (SVPE) within 2 weeks of the onset of weakness. □ Non-SVPE (n=20): twenty-four patients aged ≥ 18 -years-old with a diagnosis other than GBS who required a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period as the patients with GBS received SVPE; * p < 0.0001.

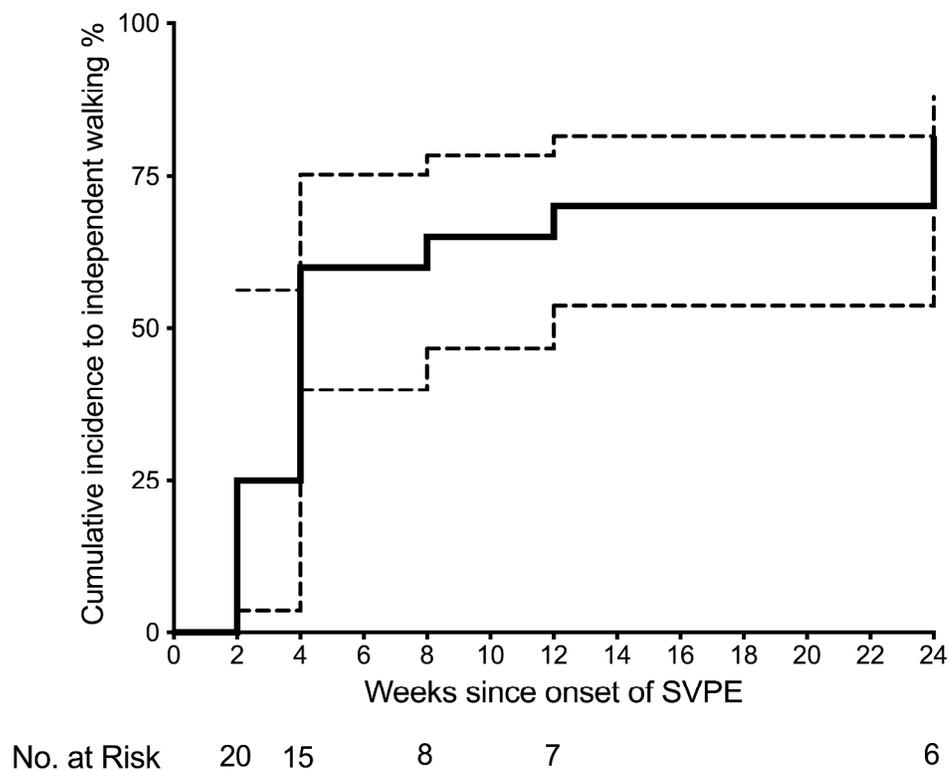
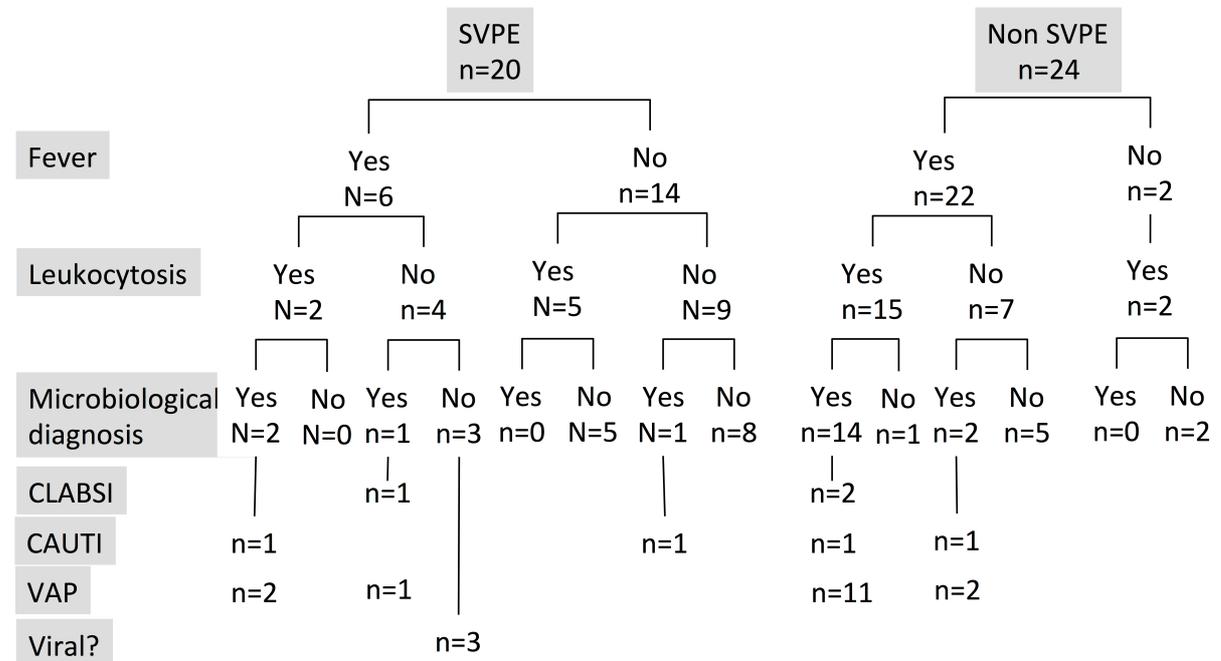


Figure 3: Kaplan-Meier estimate (with 95% confidence limits) of the cumulative incidence of restoration of independent walking ability in patients with GBS treated with SVPE.

Supplementary Figure: Hospital-acquired infections in the 20 patients with GBS treated with SVPE and the 24-hospital control patients without GBS.



SVPE: small volume plasma exchange, CLABSI: central line-associated blood stream infection, CAUTI: catheter-associated urinary tract infection, VAP: ventilator-associated pneumonia.

2017 CONSORT checklist of information to include when reporting a randomized trial assessing nonpharmacologic treatments (NPTs)*.
Modifications of the extension appear in italics and blue.

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
Title and abstract					
	1a	Identification as a randomized trial in the title	NA (Non-randomized)		
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3, 4, 5	Refer to CONSORT extension for abstracts for NPT trials	3, 4, 5
Introduction					
Background and objectives	2a	Scientific background and explanation of rationale	6		
	2b	Specific objectives or hypotheses	6, 7		
Methods					
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7	When applicable, how care providers were allocated to each trial group	NA
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	No changes to methods after trial commencement		
Participants	4a	Eligibility criteria for participants	7, 8	When applicable, eligibility criteria for centers and for care providers	NA
	4b	Settings and locations where the data were collected	7		
Interventions†	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7, 8	Precise details of both the experimental treatment and comparator	7, 8
	5a			Description of the different components of the interventions and, when applicable, description of the procedure for tailoring the interventions to individual participants.	9
	5b			Details of whether and how the interventions were standardized.	8, 9

Cite as: Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40-7.

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Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
	5c.			Details of whether and how adherence of care providers to the protocol was assessed or enhanced	8, 9
	5d			Details of whether and how adherence of participants to interventions was assessed or enhanced	NA
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9		
	6b	Any changes to trial outcomes after the trial commenced, with reasons	No changes to trial outcomes after the trial commenced		
Sample size	7a	How sample size was determined	9	When applicable, details of whether and how the clustering by care providers or centers was addressed	NA
	7b	When applicable, explanation of any interim analyses and stopping guidelines	10		
Randomization:					
- Sequence generation	8a	Method used to generate the random allocation sequence	NA (Non-randomized)		
	8b	Type of randomization; details of any restriction (such as blocking and block size)	NA (Non-randomized)		
- Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	NA (Non-randomized)		
- Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	NA (Non-randomized)		
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Blinding was not possible	If done, who was blinded after assignment to interventions (e.g., participants, care providers, those administering co-interventions, those assessing outcomes) and how	Blinding was not possible

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Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
	11b	If relevant, description of the similarity of interventions	7, 8		
	11c			If blinding was not possible, description of any attempts to limit bias	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10	When applicable, details of whether and how the clustering by care providers or centers was addressed	NA
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA		
Results					
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	11	The number of care providers or centers performing the intervention in each group and the number of patients treated by each care provider or in each center	Single center study
	13b	For each group, losses and exclusions after randomization, together with reasons	No losses and exclusions after inclusion		
	13c			For each group, the delay between randomization and the initiation of the intervention	11
	new			Details of the experimental treatment and comparator as they were implemented	11-16
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7		
	14b	Why the trial ended or was stopped	NA (Trial completed)		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1	When applicable, a description of care providers (case volume, qualification, expertise, etc.) and centers (volume) in each group.	NA
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11-12		

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Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12-16		
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	15		
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12-15		
Discussion					
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	20	In addition, take into account the choice of the comparator, lack of or partial blinding, and unequal expertise of care providers or centers in each group	NA
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	16-20	Generalizability (external validity) of the trial findings according to the intervention, comparators, patients, and care providers and centers involved in the trial	16-20
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16-20		
Other information					
Registration	23	Registration number and name of trial registry	4		
Protocol	24	Where the full trial protocol can be accessed, if available	Manuscript reference no: 17		
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	21		

*Additions or modifications to the 2010 CONSORT checklist. CONSORT = Consolidated Standards of Reporting Trials
 †The items 5, 5a, 5b, 5c, 5d are consistent with the Template for Intervention Description and Replication (TIDieR) checklist

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Table: Required documents of the safety and feasibility study of the small volume plasma exchange (SVPE) for Guillain-Barré syndrome patients for the World Health Organization Trial Registration Data Set

	Item/Label	Description
1	Primary Registry and Trial Identifying Number	Clinicaltrials.gov NCT02780570
2	Date of Registration in Primary Registry	May 23, 2016
3	Secondary Identifying Numbers	International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) Protocol Number: PR-15086, Version no. 3, Date: 09/12/2015
4	Source(s) of Monetary or Material Support	GBS/CIDP Foundation International Fondation Mérieux: (Small Grants Program 2015)
5	Primary Sponsor	GBS/CIDP Foundation International
6	Secondary Sponsor(s)	Fondation Mérieux: (Small Grants Program 2014)
7	Contact for public queries	MD. BADRUL ISLAM Email: bislamdmch@gmail.com Telephone no: +880 1712 89 0172 Postal address: Dr. Badrul Islam

		Research trainee and PhD Fellow Laboratory Sciences and Services Division (LSSD) Icddr,b Dhaka, Bangladesh
8	Contact for scientific queries	MD. BADRUL ISLAM Principal Investigator (PI) Email: bislamdmch@gmail.com Telephone no: +880 1712 89 0172 Postal address: Dr. Badrul Islam Research trainee and PhD Fellow Laboratory Sciences and Services Division (LSSD) Icddr,b Dhaka, Bangladesh
9	Public title	Small volume plasma exchange for Guillain-Barré syndrome
10	Scientific title	Small volume plasma exchange for Guillain-Barré syndrome in low-income countries: a safety and feasibility study
11	Countries of Recruitment	Bangladesh
12	Health condition(s) or problem(s) studied	Guillain-Barré syndrome (GBS)
13	Interventions	<u>Small Volume Plasma Exchange (SVPE)</u> A loading dose of low-molecular weight heparin (1.5 mg/kg) will be given subcutaneously at least two hours

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3 before initiation of SVPE; the same dose will be
4 administered once daily or divided into two equal doses
5 daily for eight days or until SVPE is completed. Whole
6 blood (7 mL/kg body weight) will be drawn from the
7 central venous catheter into the blood transfusion bag
8 in each session. The blood bag will be hung beside the
9 patient for 2.5 h on a saline stand and left
10 uninterrupted to allow plasma and blood cells to
11 separate. The blood cells will be infused back into the
12 patient and plasma will be discarded and replaced with
13 fresh frozen plasma and colloid solution alternately (in
14 equal volumes) via the closed-circuit SVPE kit illustrated
15 in. In case of excessive clotting (bleeding time reduction
16 of > 50% of baseline for that patient), aspirin (600 mg)
17 will be administered orally at least two hours before
18 the next SVPE session and continued thereafter at 150
19 mg orally/day until SVPE is completed. One blood bag
20 will be used each day, with a total of six sessions/day. A
21 total of 48 sessions will be performed over eight days,
22 removing approximately 8000 mL plasma in total.
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39 Central venous catheterized patients without GBS

40 To compare the safety of SVPE in patients with GBS in
41 the context of the background risk of central line-
42 associated blood stream infection (CLABSI) at the study
43 intensive care (ICU) and high-dependency care (HDU)
44 units, the incidence of CLABSI will be assessed in a
45 control group of adult patients with a diagnosis other
46 than GBS admitted to the same ICU and HDU units in
47 the same period of time the patients with GBS will be
48 enrolled for SVPE. We will assess the rate of CLABSI in
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		<p>patients aged ≥ 18-years-old requiring a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units.</p>
14	Key Inclusion and Exclusion Criteria	<p><u><i>Inclusion criteria for SVPE in GBS patients</i></u></p> <ol style="list-style-type: none"> 1. Patients aged ≥ 18-years-old fulfilling the diagnostic criteria for GBS of the National Institute of Neurological and Communicative Disorders and Stroke (NINDS) 2. Unable to walk unaided for more than 10 meters (GBS disability score ≥ 3) 3. Presented within 2 weeks of the onset of weakness 4. Unable to afford standard treatment with IVIg or PE. <p><u><i>Exclusion criteria for SVPE in GBS patients</i></u></p> <ol style="list-style-type: none"> 1. Patients with severe or terminal concomitant illness 2. Evidence of healthcare-associated infection on admission (except for aspiration pneumonia) 3. Previous history of severe allergic reaction to properly matched blood products and pregnant women will be excluded from the study. <p><u><i>Inclusion criteria for patients without GBS</i></u></p> <ol style="list-style-type: none"> 1. Patients aged ≥ 18-years-old 2. Requiring a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period of time the patients with GBS enrolled for SVPE. <p><u><i>Exclusion criteria for patients without GBS</i></u></p>

		<ol style="list-style-type: none"> 1. Patients with healthcare-associated infection present on admission (except aspiration pneumonia) 2. Pregnant women
15	Study type	<p><u>Type of the study:</u> Interventional</p> <p><u>Method of allocation:</u> Non-randomized</p> <p><u>Masking:</u> Non-masked</p> <p><u>Assignment:</u> Parallel arm</p> <ul style="list-style-type: none"> • SVPE in patients with GBS • Rate of CLABSI in patients without GBS <p><u>Purpose:</u> Safety and feasibility of SVPE</p>
16	Date of first enrolment	February 20, 2016
17	Target sample size	<p>SVPE in patients with GBS = 20</p> <p>Rate of CLABSI in patients without GBS = ≥ 20</p>
18	Recruitment status	<p>Completed:</p> <ul style="list-style-type: none"> • Twenty cases of GBS have been successfully treated with SVPE and 24 control cases without GBS have been recruited.
19	Primary Outcome(s)	<p><u>Primary outcome of safety:</u></p> <ol style="list-style-type: none"> 1. Number of patients with GBS treated with SVPE developing severe sepsis or septic shock due to central line associated blood stream infection (CLABSI) as per standard guideline (Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central line-associated Bloodstream Infection); CDC Device-associated Module, BSI. January 2017) 2. Occurrence of venous thrombosis in the limb

		<p>where the CVC is placed. Venous thrombosis will be assessed according to Wells criteria (Philip S. Wells et al. Evaluation of d -Dimer in the Diagnosis of Suspected Deep-Vein Thrombosis; N Engl J Med 2003;349:1227-35)</p> <p><u>Primary outcome of feasibility:</u></p> <ol style="list-style-type: none"> 1. Ability to remove at least eight litres of plasma by SVPE over eight days.
20	Secondary Outcome(s)	<p><u>Secondary outcome of safety:</u></p> <ol style="list-style-type: none"> 2. Relative risk of CLABSI due to SVPE compared to CLABSI in control patients without GBS treated using a CVC 3. Hemodynamic instability during the SVPE procedure (variations in systolic blood pressure greater than 30 mmHg or sudden bradycardia involving a reduction in heart rate by more than 20 beats per min within 30 min of starting SVPE or an increase in heart rate above 120 beats per min) 4. Development of anaemia (Hb <7 gm/dL) or serious haemorrhage requiring blood transfusion. <p><u>Secondary outcome of feasibility:</u></p> <ol style="list-style-type: none"> 1. Rate of CVC occlusion during the SVPE procedure 2. The healthcare personnel's acceptability and

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3 satisfaction with the SVPE procedure and any
4 unanticipated events compromising the SVPE
5 procedure as assessed using a standard
6 questionnaire.
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10 3. Neurological outcome will be assessed in terms
11 of improvement in GBS disability score and MRC
12 sum score at discharge and up to 4 weeks after
13 entry.
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BMJ Open

Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings: a phase II safety and feasibility study

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Medical management
Keywords:	Guillain-Barré syndrome, Small volume plasma exchange, Safety, Feasibility
<p>Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.</p> <p>SUPPLEMENTARY VIDEO.mp4</p>	

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5 2 Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings:
6
7 3 a phase II safety and feasibility study
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3 50 **ABSTRACT**

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5 51 **OBJECTIVE**

6
7 52 To assess the safety and feasibility of small volume plasma exchange (SVPE) as an alternative to
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9 53 standard plasma exchange (PE) or intravenous immunoglobulin (IVIg) for Guillain-Barré
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11 54 syndrome (GBS) patients.

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14 55 **DESIGN**

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16 56 Non-randomized, single arm, interventional trial.

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18 57 **SETTING**

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20 58 National Institute of Neurosciences and Hospital, Dhaka, Bangladesh.

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22 59 **PARTICIPANTS**

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24 60 Twenty adult (>18 years) patients with GBS presented within 2 weeks of onset of weakness who
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26 61 were unable to walk unaided for more than 10 meters.

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29 62 **INTERVENTIONS**

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31 63 SVPE involves blood cell sedimentation in a blood bag and removal of supernatant plasma after
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33 64 blood cells are re-transfused. This procedure was repeated three to six times a day, for eight
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35 65 consecutive days.

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38 66 **OUTCOME MEASURES**

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40 67 Serious adverse events (SAE) were defined as severe sepsis and deep venous thrombosis related
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42 68 to the central vein catheter (CVC) used during SVPE. SVPE was considered safe if less than 5/20
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44 69 patients experienced a SAE, and feasible if 8 L plasma could be removed within 8 days in at least
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46 70 15/20 patients.

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48 71 **RESULTS**

49
50 72 Median patient age 33 years (IQR 23-46; range 18-55); 13 (65%) were male. Median MRC sum
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52 73 score was 20 (IQR 0-29; range 0-36); three (15%) patients required mechanical ventilation. One
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54 74 patient developed SAE (severe sepsis, possibly related to CVC). Minor adverse effects were

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3 75 transient hypotension in 10 (50%) patients; CVC-associated bleeding in 10 (50%); transfusion
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5 76 reaction to fresh frozen plasma in 4 (20%); and hypo-albuminemia, anaemia or electrolyte
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7 77 imbalance in 4 (20%). Removal of 8 L plasma was possible in 15 (75%) patients. GBS disability
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9 78 score improved by at least one grade in 14 (70%) patients four weeks after SVPE started. No
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11 79 patients died.

13 80 CONCLUSION

15 81 SVPE seems a safe and feasible alternative treatment to standard PE or IVIg for GBS; further
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17 82 studies of clinical efficacy in low-resource developing countries are warranted.
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22 84 TRIAL REGISTRATION

24 85 Clinicaltrials.gov NCT02780570 on May 23, 2016
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3 94 **Strength and limitations of the study:**
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7 96 1. The strength of this study underlies the novel and simple technique of SVPE, which is
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9 97 much less expensive than conventional immunotherapies (plasma exchange and
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11 98 intravenous immunoglobulin)

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13 99 2. SVPE is corroborated as safe and feasible for the first time in a prospective and
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15 100 standardized cohort of patients with Guillain-Barré syndrome (GBS).

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18 101 3. The intrinsic limitations of this study are its non-randomized, single arm nature, which is
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20 102 conducted in a single center with a limited sample size of GBS patients.

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22 103 4. Clinical efficacy of SVPE on patients with GBS was a secondary end-point assessment
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24 104 and therefore deserves a randomized controlled trial in future to assess the clinical
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26 105 efficacy of SVPE for the patients with GBS.
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107 **Introduction**

108 Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy with a
109 yearly incidence of 1.2 to 2.3 cases per 100,000 per year.¹ GBS is characterized by rapidly
110 progressive limb weakness and, in a proportion of cases, respiratory failure (25%) or severe
111 autonomic dysfunction (10%). Plasma exchange (PE) was the first treatment proven to be
112 effective for GBS, if given within 4 weeks of the onset of weakness.²⁻¹¹ Conventionally for GBS
113 patients, three to five plasma exchange sessions are done in alternate days within a span of 7 to
114 14 days targeting a plasma exchange rate of 120 - 200 ml/kg (40-50ml/kg/day).⁷ Later studies
115 showed treatment with intravenous immunoglobulin (IVIg) (0.4 g/kg per day for 5 days) has a
116 similar efficacy as PE in patients with GBS who are unable to walk, if started within 2 weeks of
117 the onset of weakness.^{12 13}

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119 Unfortunately, most patients in low-income countries cannot afford expensive treatment with
120 either PE or IVIg.¹⁴ In Bangladesh, a full course of IVIg for a 60 kg adult costs approximately
121 12,000-16,000 US\$ and treatment with conventional PE for 5 days costs approximately 4,500-
122 5,000 US\$. The mean income in Bangladesh was 4 US\$ per day in 2016 (World Bank and
123 Bangladesh Bureau of Statistics 2016); IVIg and PE cost the equivalent of 3,000 and 1,250 mean
124 income days, respectively. At present, the majority (92%) of patients with GBS in Bangladesh
125 receive supportive care only.¹⁴ In addition, mobile PE equipment is not available in Bangladesh;
126 therefore, patients admitted to the intensive care unit (ICU) cannot receive PE. We previously
127 reported the mortality rates for GBS in Bangladesh range from 12 to 14% and observed 29% of
128 patients with GBS in Bangladesh are unable to walk at 6 months after onset; these poor outcomes
129 are undoubtedly due to the low rates of specific treatment with PE or IVIg.^{15 16}

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3 131 Small volume plasma exchange (SVPE) may represent a cheap, effective alternative treatment for
4
5 132 GBS. SVPE is based on the same principle as conventional PE (selective removal of plasma) but
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7 133 uses a novel, simple technique with much lower costs (approximately 500 US\$). The current non-
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9 134 randomized trial was designed to investigate the safety and feasibility of SVPE in 20 patients
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11 135 with GBS admitted to the National Institute of Neurosciences Hospital in Dhaka, Bangladesh.
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15 16 137 **Methods/Design**

17 18 138 *Study design*

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20 139 For this non-randomized, single arm, interventional safety and feasibility trial, 20 adult patients
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22 140 with GBS were enrolled between March 2016 and December 2016 for SVPE at the National
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24 141 Institute of Neurosciences and Hospital (NINS), Dhaka, Bangladesh. A detailed study protocol
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26 142 was published previously and includes definitions of all variables used in this study.¹⁷
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31 144 Four to six daily sessions of whole blood sedimentation and removal of supernatant plasma after
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33 145 re-transfusion of the sedimented blood cells was planned for the 20 patients with GBS, with a
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35 146 target of removing an overall volume of at least 8 litres (L) of plasma over a total of 8 days.¹⁷
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37 147 (See supplementary video for SVPE procedure)
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42 149 Patients with GBS were monitored according to a standard protocol throughout the course of
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44 150 SVPE until the second day after withdrawal of the central venous catheter (CVC) in order to
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46 151 assess predefined measures of safety and feasibility and followed up for six months to assess
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48 152 neurological outcome. The protocol was reviewed and approved by the institutional research and
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50 153 ethics review committees at the icddr,b and registered at clinicaltrials.gov (NCT02780570).¹⁷ All
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52 154 patients provided written informed consent to participate in this study.
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3 156 *Patient and Public Involvement*
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5 157 Patients and or public were not involved either in the development of the research question, study
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7 158 design and outcome measure or recruitment to and conduct of the study.
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11 160 *Inclusion and exclusion criteria for patients with GBS*
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13 161 Patients aged ≥ 18 -years-old fulfilling the diagnostic criteria for GBS of the National Institute of
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15 162 Neurological and Communicative Disorders and Stroke (NINDS)¹⁸ were enrolled, provided they
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17 163 were unable to walk unaided for more than 10 meters (GBS disability score ≥ 3), presented
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19 164 within 2 weeks of the onset of weakness, and were unable to afford standard treatment with IVIg
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21 165 or PE. Patients with concomitant severe or terminal illnesses, evidence of healthcare-associated
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23 166 infection (HAI) on admission (except for aspiration pneumonia), a previous history of severe
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25 167 allergic reactions to properly matched blood products, and pregnant women were excluded from
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27 168 the study.
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33 170 *Control cohort*
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35 171 To compare the safety of SVPE in patients with GBS in the context of the background risk of
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37 172 central line-associated blood stream infection (CLABSI) at our institution, we prospectively
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39 173 assessed the incidence of CLABSI in a hospital control group of 24 adult patients without GBS
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41 174 receiving neurocritical care. Hospital controls were eligible based on the following
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43 175 characteristics: ≥ 18 -years-old, a neurological diagnosis other than GBS, and a CVC placed for $>$
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45 176 2 and ≤ 8 calendar days after admission to the same ICU or HDU unit as the SVPE-treated
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47 177 patients. Patients with a HAI (except aspiration pneumonia) and pregnant women were excluded
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49 178 from the control group.
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3 181 *Primary and secondary outcome measures*

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5 182 The primary outcome measures of safety were the number of patients with GBS treated with
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7 183 SVPE who developed either severe sepsis or septic shock due to CLABSI¹⁹ and the occurrence of
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9 184 venous thrombosis in the limb where the CVC was placed. The primary outcome measure of
10
11 185 feasibility was the ability to remove at least 8 L of plasma over 8 days.

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13 186 The secondary outcome measures of the safety of SVPE were the relative risk of CLABSI due to
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15 187 SVPE (compared to CLABSI in the hospital control group without GBS), hemodynamic
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17 188 instability during the SVPE procedure, and development of anaemia (Hb < 8 gm/dL) or any
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19 189 catheter-related haemorrhage requiring a blood transfusion.

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21 190 The secondary outcome measure of feasibility of SVPE was the rate of CVC occlusion during the
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23 191 SVPE procedure. In addition, neurological outcome was assessed using the GBS disability
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25 192 score²⁰, MRC sum score²¹, Overall Neuropathy Limitation Scale (ONLS)²² and Rasch-built
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27 193 Overall Disability Scale (R-ODS)²³ at 1st, 2nd, 3rd, and 6th months from the start of SVPE.

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33 195 *Procedure safety documentation and cost of SVPE*

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35 196 Strict aseptic procedures were followed to prevent CLABSI.²⁴⁻²⁶ SVPE was documented in terms
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37 197 of the duration and amount of plasma removed in each session, and the type and volume of
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39 198 replacement fluid and fresh frozen plasma (FFP) used. Throughout the procedure, the
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41 199 haemodynamic, haematological, biochemical, coagulation and infection profiles of the SVPE-
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43 200 treated patients were monitored according to the protocol.¹⁷ Screening for hepatitis B and C
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45 201 viruses, human immunodeficiency virus (HIV) and syphilis were performed as patient baseline
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47 202 assessments, and also on donor FFP before administration. CLABSI, primary and secondary
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49 203 bloodstream infections¹⁹, catheter-associated urinary tract infection (CAUTI)²⁷, ventilator-
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51 204 associated pneumonia (VAP)²⁸ and other HAI^{29 30} were documented in the SVPE-treated patients
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53 205 with GBS and the hospital control group. Expenditure for the full course of SVPE will be
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3 206 approximately 500 US\$ [fresh frozen plasma (24 bags) = 240 US\$, blood bag and saline sets: 40
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5 207 US\$, low molecular weight heparin: 110 US\$, routine investigation: 50 US\$, saline: 10 US\$, CV
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7 208 catheter: 40 US\$ = total 490 US\$].
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11 210 *Sample size*

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13 211 This safety and feasibility study enrolled 20 patients with GBS for SVPE. We could not
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15 212 perform a formal power calculation for this safety and feasibility study. The sample size
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17 213 was based on previous pilot studies conducted in GBS.^{31 32} The baseline rate of CLABSI
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19 214 was measured in the hospital control group of 24 patients without GBS admitted to the
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21 215 same study facility who required a CVC for at least 8 days during the study period.
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26 217 *Stopping rules for the trial based on safety and feasibility*

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28 218 Decision to stop the SVPE trial was designated using a Bayesian approach.³³⁻³⁵
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30 219 Accordingly, a predictive success rate of 75% was predefined for the SVPE procedure. If
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32 220 more than 5 of 20 patients experienced an SAE, or if it appeared impossible to remove at
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34 221 least 8 L of plasma over 8 days in at least 15 of 20 patients, the procedure was considered
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36 222 unsafe or unfeasible.
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42 224 *Statistical analysis*

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44 225 The rate of HAIs (CLABSI, VAP and CAUTI) per 1000 device days were calculated by
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46 226 dividing the number of each HAI during the study period by the number of device days and
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48 227 multiplying the result by 1000. The infection safety profile for SVPE was assessed by
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50 228 calculating the standardized infection ratio to define the risk of HAIs in patients with GBS
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52 229 treated with SVPE. The standardised infection ratio (SIR) was calculated by dividing the
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54 230 number of observed HAI by the number of HAI predicted (i.e., the infection rate in the control
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231 group). The predicted HAI rate was calculated using the rates of HAI in the hospital control
232 group of patients without GBS during the study period. Percentage values were compared using
233 the Chi-square test or Fisher's exact test (two-tailed) and median values, the Mann-Whitney U-
234 test using SPSS 22 software (IBM SPSS Statistics for Windows Version 22.0., IBM Corp.,
235 Armonk, NY, USA). Analyses were performed on an intention-to treat basis. All *P*-values
236 reported are two-sided; $p < 0.05$ was considered significant.

237

238 **Results**

239 *Patients and hospital controls*

240 The demographic and clinical characteristics of the 20 patients with GBS are given in Table 1.
241 The median age of the patients with GBS was 33 years (range; 18-55); median body weight was
242 60 kg (IQR, 55-65 kg; range, 50-72 kg) and 13 (65%) patients were male (Fig. 1). On admission
243 and before the start of SVPE, all 20 patients with GBS were unable to walk independently (GBS
244 disability score, 4). One patient required mechanical ventilation from the second day after the
245 onset of weakness; SVPE was started on the fourth day of mechanical ventilation (patient 9, Fig.
246 1). Two of the 19 patients who did not require mechanical ventilation at the start of the study
247 required mechanical ventilation on the second day after initiation of SVPE (patients 11 and 19,
248 11 and 2 days after the onset of weakness, respectively; Fig. 1). The median MRC sum score for
249 the limb muscles in all 20 patients was 20 (IQR: 0-29; range: 0-36; Fig. 1). Symptoms of a
250 preceding infection in the 4 weeks before the onset of weakness were present in 18 (90%)
251 patients with GBS, of whom 10 (50%) had diarrhoea. Median duration from admission to start of
252 SVPE was two days (IQR, 2-3 days; range, 0-7 days). Median duration to nadir from the onset of
253 weakness was five days (range, 1-13 days). Electrodiagnostic nerve conduction studies indicated
254 15 (75%) patients had an axonal subtype and 5 (25%) patients had a demyelinating subtype of
255 GBS. Median duration from onset of weakness to NCS examination was 10 days (range, 4-16

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3 256 days). All patients had albuminocytologic dissociation; median CSF protein was 166 mg/dL
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5 257 (range 117-253 mg/dL). Median duration from onset of weakness to CSF examination was 11
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7 258 days (range, 4-17 days).

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11 260 Median age of the 24 hospital control patients without GBS was 44 years (IQR, 25-57; range; 18-
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13 261 74); 10 (42%) were male. Age and gender distribution were not significantly different compared
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15 262 to the 20 patients with GBS ($p = 0.2155$, $p = 0.1434$, respectively). The diagnoses for these 24
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17 263 patients were: brain tumour ($n = 5$), transverse myelitis ($n = 5$), head trauma after road traffic
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19 264 accident ($n = 3$), viral meningoencephalitis ($n = 2$), myasthenia gravis ($n = 2$), compressive
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21 265 cervical myelopathy ($n = 2$), cerebrovascular accident ($n = 2$), motor neuron disease ($n = 1$),
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23 266 electrolyte imbalance ($n = 1$) and status epilepticus ($n = 1$).

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27 28 29 268 *Primary endpoints*

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31 269 One patient with GBS treated with SVPE developed severe sepsis, possibly due to SVPE-related
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33 270 CLABSI (SVPE window-period blood culture revealed methicillin-resistant *Staphylococcus*
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35 271 *aureus*). This patient required intravenous fluid, noradrenalin infusion and intravenous
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37 272 antibiotics, but eventually improved (patient 11, Fig. 1). This patient also had signs and
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39 273 symptoms suggestive of aspiration pneumonia and VAP; *Streptococcus spp.* was isolated from
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41 274 pulmonary aspirates. Further laboratory results revealed dys-electrolytemia, anaemia and hypo-
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43 275 albuminemia. No patients experienced deep vein thrombosis due to the CVC for SVPE. Fifteen
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45 276 (75%) of the 20 patients met the primary endpoint of feasibility, defined as the ability to remove
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47 277 at least 8 L of plasma in eight days. The median volume of plasma removed was 8.5 L (IQR, 7.9-
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49 278 8.8 L; range, 6.3-9.6 L; Fig. 1). The median plasma exchange rate was 140 mL/kg bodyweight
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51 279 (IQR, 125-155 mL/kg; range, 110-175 mL/kg) over 8 days and 16 (80%) patients had a plasma
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53 280 exchange rate > 120 mL/kg (Table 2).

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3 281 *Secondary endpoints*

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5 282 *Infections among SVPE-treated patients with GBS and hospital controls*

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7 283 Among the 20 patients with GBS treated with SVPE, six (30%) had fever during SVPE (Fig. 1,
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9 284 Supplementary Figure 1), including 2 (10%) patients with leucocytosis who were diagnosed with
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11 285 HAI (VAP and CAUTI in one patient; VAP in one patient). In three out of four (20%) patients
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13 286 with fever without leucocytosis, fever subsided within two to three days without antimicrobial
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15 287 therapy (Fig. 1). The remaining patient with pyrexia without leucocytosis had microbiological
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17 288 evidence of both CLABSI and VAP (patient 11, Fig. 1). In all other 14 patients with GBS, no
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19 289 fever was documented during the course of SVPE until the tenth day of SVPE (second day after
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21 290 removal of the CVC for SVPE). Five of these 14 patients had leucocytosis, but no site-specific
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23 291 HAI could be detected. However, one of the nine patients without fever but leucocytosis fulfilled
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25 292 the criteria for CAUTI (patient 12, Fig. 1). All three patients who required mechanical ventilation
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27 293 subsequently developed VAP; two of the 13 patients who required a urinary catheter developed a
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29 294 CAUTI (patient 11, Fig. 1). No patients died during the 6 months follow-up.

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35 296 All 24-hospital control patients without GBS required mechanical ventilation and an indwelling
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37 297 urinary catheter. Of these patients, 22 (92%) patients had fever, of whom 15 (63%) had
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39 298 leucocytosis; a diagnosis of a specific HAI could be made 14 of these 15 patients (CLABSI in
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41 299 two, CAUTI in one, VAP in 11) and four (17%) fulfilled the criteria for severe sepsis
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43 300 (Supplementary Figure 1). Seven (29%) of the 24 hospital control patients had fever without
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45 301 leucocytosis. In two of these seven patients, a specific HAI was diagnosed (CAUTI and VAP in
46
47 302 one, and VAP in one). In two hospital control patients, no fever was documented until day 10
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49 303 after first placement of the CVC, but leucocytosis was present and no site-specific HAI could be
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51 304 detected (Supplementary Figure 1).

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3 306 The rates of CLABSI, CAUTI and VAP per 1000 device days in the SVPE-treated patients with
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5 307 GBS were 6.25, 19.2 and 40 compared to 10.4, 10.4 and 67.7 for the hospital control patients
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7 308 without GBS, respectively. The relative risks of CLABSI, CAUTI and VAP associated with
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9 309 SVPE were 0.6, 1.2 and 1.8, respectively, compared to hospital control patients. The rates of
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11 310 CLABSI, CAUTI and VAP were comparable between SVPE-treated patients with GBS and
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13 311 hospital control patients ($p > 0.05$). Antimicrobial agents were used more frequently in the
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15 312 hospital control patients ($p < 0.0001$; Fig. 2). The standardised infection ratios for CLABSI,
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17 313 CAUTI and VAP for SVPE-treated patients with GBS were 0.6, 1.8 and 1.9, respectively.
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21 315 *Other secondary endpoints*

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24 316 Ten (50%) of the 20 patients treated with SVPE experienced transient hypotension during SVPE,
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26 317 which was corrected by infusion of 200-300 mL crystalloid saline (Fig. 1). Minor bleeding
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28 318 through the CVC insertion site (excluding at the time of insertion) was observed in 10/20 patients
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30 319 (50%; Fig. 1); these bleeds required a pressure pack. Reduction of the anticoagulant dose along
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32 320 with a pressure pack was required in 3/20 patients, who all had a prolonged prothrombin time
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34 321 (PT). Three patients had single episode of haemorrhage through the urinary catheter: one was
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36 322 diagnosed with a CAUTI with normal coagulation profile, one had a prolonged PT, the other had
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38 323 sterile haematuria with normal PT. Overall, PT and activated partial thromboplastin time (aPTT)
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40 324 were prolonged in 4/20 patients and only PT was prolonged in 2/20 patients. Clotting time and
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42 325 bleeding time were not prolonged in any patient. One patient developed anaemia (haemoglobin, 8
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44 326 gm/L) at the end of SVPE; this patient also had severe sepsis and required one unit of blood
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46 327 transfusion (patient 11, Fig. 1). CVC blockages were not observed in any SVPE-treated patients
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48 328 with GBS. One patient with increased clotting tendency who required an increased dose of low
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50 329 molecular weight heparin had shortened clotting time (CT) ($< 50\%$ of upper limit of normal),
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52 330 though PT was normal (patient 10, Fig. 1).
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3 331 The neurological outcomes of the SVPE-treated patients with GBS at six months in terms of
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5 332 neurological scores are given in Table 3. Median time to recover the ability to walk unaided was
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7 333 4 weeks (Fig. 3). Fourteen (70%) of the 20 patients had an improvement in GBS disability score
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9 334 of one or more grades at four weeks after the onset of SVPE. At one month, 12 patients (60%)
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11 335 were able to walk unaided, two patients (10%) were able to walk aided and six (30%) patients
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13 336 were bedbound, of whom three still required mechanical ventilation. At three months, 14 (70%)
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15 337 patients were able to walk unaided, one (5%) could walk with aid and five (25%) patients were
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17 338 bedbound. At six months, 14 (70%) patients were able to walk unaided, three (5%) could walk
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19 339 with aid and three (15%) remained bedbound (Table 3).
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25 341 *Other relevant clinical and laboratory findings*

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27 342 Allergic/transfusion reaction to FFP was observed in four patients with GBS treated with SVPE
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29 343 (Fig. 1). These transfusion reactions presented as an itchy erythematous skin rash (three patients),
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31 344 fever (two patients), hypotension (one patient) following transfusion of FFP; all of these reactions
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33 345 were managed with oral antihistamine (and intravenous saline in one patient) without further
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35 346 complications.
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40 348 The other documented haematological and biochemical abnormalities were hypo-albuminemia (n
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42 349 = 4), thrombocytopenia ($n = 6$), hyponatraemia ($n = 1$), hypokalaemia ($n = 3$), hypomagnesaemia
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44 350 ($n = 1$), hypocalcaemia ($n = 3$); (Table 2).
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49 352 *Immunoglobulin dosage admitted by FFP*

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51 353 During SVPE the median volume of FFP received per GBS patient as replacement fluid was
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53 354 6000 ml (range, 5000 ml to 6000 ml). Considering the normal plasma IgG level of 11.20 mg/ml
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3 355 (range, 6.9 mg – 17.6 mg)³⁶, SVPE treated GBS patients received IgG dose of median 0.9 g/kg
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5 356 (range 0.6 g/kg – 1.3 g/kg).
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9 358 **Discussion**

11 359 *Principal findings*

13 360 This study suggests SVPE may represent a safe and feasible alternative to conventional plasma
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15 361 exchange for patients with severe GBS in limited-resource settings. Of the 20 patients in this
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17 362 study, one (5%) experienced a SAE (severe sepsis due to probable CLABSI). The rate of SAE
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19 363 was not significantly higher than the hospital control group without GBS with a CVC, and no
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21 364 patients had a CVC-related thromboembolic event in patients with SVPE. We were able to
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23 365 remove the prespecified target volume (8 L) of plasma as the target primary endpoint of
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25 366 feasibility in 15/20 (75%) patients with GBS. Median plasma exchange volume and rate during
26
27 367 SVPE were 8.4 L and 140 mL/kg, respectively. Minor adverse effects included transient
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29 368 hypotension during SVPE in 50% (10/20), minor haemorrhage from CVC insertion site in 50%
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31 369 (10/20), transfusion reaction to fresh frozen plasma in 20% (4/20), and hypo-albuminemia,
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33 370 anaemia and electrolyte imbalance in 20% (4/20) of patients. An improvement of at least one
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35 371 grade on the GBS disability score was observed for 14/20 (70%) patients at four weeks after the
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37 372 initiation of SVPE. No patients died.
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44 374 *Comparison with baseline hospital control patients and standard/modified PE*

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46 375 With respect to HAIs, no significant differences were observed in the frequency of CLABSI,
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48 376 severe sepsis, VAP or CAUTI between the SVPE-treated patients with GBS and 24 hospital
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50 377 control patients without GBS treated using a CVC in the same ICU or HDU (Fig. 2). However,
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52 378 antimicrobial agents were used more frequently, usually prophylactically, in the hospital control
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54 379 patients compared to the patients with GBS treated with SVPE ($p < 0.0001$; Fig. 2). The
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3 380 probability of detecting microorganisms in clinical infections may have been reduced due to
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5 381 overzealous use of antibiotics in the hospital control patients. Early trials of PE in patients with
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7 382 GBS showed 34% of patients develop severe infections.^{7 11} Subsequently, another large trial
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9 383 documented septicaemia in 19% of patients.⁵ However, the rates of CLABSI were not reported.

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13 385 A previous RCT on GBS from the US showed a beneficial effect with PE rate of 40-50
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15 386 ml/kg/session, for 3 to 5 sessions in 7 to 14 days, which comes to a total PE volume of 120-250
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17 387 ml/kg.⁷ The first French RCT on adult GBS patients showed beneficial effect of 4 PE sessions [2
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19 388 plasma volume (3.5 L) per PE session] over 8 days and in range, 6 – 12 L plasma was removed
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21 389 per patient.⁴ Subsequent French RCT with PE dose escalation showed, 2 PE sessions [1.5 plasma
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23 390 volume per PE session] is beneficial in mild to moderate GBS cases but less effective than 4 PE
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25 391 sessions in severe GBS cases and 6 PE sessions are as effective as 4 PE sessions in severe cases
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27 392 of GBS.⁵ In this RCT the exact total plasma volume exchanged per patient was not mentioned,
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29 393 but the authors indicated that the rate of plasma exchange was 40-ml/kg body weight per PE
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31 394 session. As to that a 60-70 kg person should have an exchange of 2.4 L-2.8 L per session and the
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33 395 therapeutic range of plasma volume to be exchanged would be 5.6 L to 11.2 L ml (2 to 4 PE
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35 396 sessions).

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41 398 During the piloting of the SVPE procedure we assessed that removal of 1 L of patient plasma
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43 399 could be feasible in a day. Therefore we defined our target plasma volume of 8 L to be removed
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45 400 in 8 days. The median total PE volume and rate in SVPE was 8.4 L and 140 ml/kg, which is
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47 401 within the same range as in both the French and American RCT on PE for adult GBS patients.
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49 402 We were able to remove >120 mL/kg plasma in 80% of patients, which should provide a
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51 403 therapeutic effect.³⁷ Notably, the body weight of our patients may be lower than that of patients
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3 404 in western countries. In addition, SVPE was complete within 8 days, shorter than the usual time
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5 405 required for a full session of PE (10 to 12 days).

6
7 406 Replacement fluid used in SVPE was FFP. We have several justifications in favour of using FFP
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9 407 instead of human albumin or other available colloidal solutions available in Bangladesh. First
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11 408 FFP is safe in terms of microbiological safety since stringent screening for viral and bacterial
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13 409 contamination was performed before infusion. Second, in contrast to human albumin and colloid
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15 410 solutions, FFP contains normal human IgG that could contribute beneficial immunotherapeutic
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17 411 effect in GBS and previously used as replacement fluid in large PE trials, quintessentially with
18
19 412 the same volume (half the volume of replacement fluid) we used in SVPE.⁴⁵ SVPE treated GBS
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21 413 patients received approximately half the amount of IgG from the FFP used as replacement fluid
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23 414 compared to the total IVIg doses traditionally used in GBS (2gm/kg). Third, FFP contains all
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25 415 human plasma proteins that helps preservation of plasma colloid osmotic pressure and prevents
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27 416 formation of oedema and hypotension. Lastly FFP is much cheaper than commercial human
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29 417 albumin.

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35 419 In each day three units of FFP were transfused as replacement fluid after the last session of SVPE
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37 420 and in the initial two to three sessions, normal saline was used as replacement fluid. This was
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39 421 done to achieve the maximum immunotherapeutic effect of FFP as SVPE was not resumed before
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41 422 the next day and the IgG in FFP remained in the circulation overnight for a longer period of time
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43 423 (10 to 12 hours). However due to long half life of IgG, substantial amount of IgG present in FFP
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45 424 were probably washed away due to repeated plasma removal both during SVPE and standard PE.

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50 426 In GBS, treatment with modified methods of PE done previously, were device based and done on
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52 427 limited number of GBS patients. In one study on 25 GBS patients from India, daily removal of
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54 428 small volume of plasma (10-15 ml plasma/kg body weight) for duration of median 3 days using

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3 429 traditional PE machine was shown to be clinically beneficial.³⁸ In another study from the same
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5 430 country, 12 GBS patients were treated with PE over 10 days using different PE-machine kit
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7 431 (REF627 kit from Haemonetics Corporation Limited on MCS+ machine) where authors claimed
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9 432 clinical improvement, however the main focus was on cost effectiveness and the total plasma
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11 433 volume exchanged per patient was not mentioned.³⁹ Nevertheless these methods are based on
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13 434 specific devices those are not in common practice, nor the trained personnel for these are
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15 435 available in the developing countries.
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20 437 Important observations in terms of secondary endpoints were transient hypotension, transfusion
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22 438 reaction to FFP and minor bleeding through the CVC insertion site. Hypotension is a common
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24 439 complication during traditional PE that affects nearly half of patients.⁵ Spells of hypotension
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26 440 during SVPE were more frequent during the three to four days after initiation of SVPE, and could
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28 441 be easily corrected by rapid infusion of 300-400 mL saline (Fig. 1). The hypotension could
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30 442 possibly be explained by hypovolemia due to drawing blood or as a result of the compromised
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32 443 autonomic nervous system in patients with GBS. As SVPE proceeded, hypotensive spells were
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34 444 encountered less frequently despite drawing the same volume of blood, which may in part be
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36 445 explained by adaptation of the vasomotor system or recovery from autonomic dysfunction. Minor
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38 446 bleeding through the CVC insertion site occurred in 50% of patients and could be controlled by
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40 447 applying a simple pressure pack over the CVC insertion site in most cases; mild prolonged PT
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42 448 was noted in 30% (3/10) patients. However, spontaneous bleeding usually occurs if the PT is
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44 449 more than 2.5 times prolonged and PC is < 0.50 lac/ μ L.⁴⁰ Movement of the limb where the CVC
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46 450 was placed may have caused traction on the CVC and contributed to local bleeding in the other
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48 451 seven patients. Haematuria is not uncommon in patients with a UTI, as may have occurred in one
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50 452 SVPE treated patient; traumatic traction of the urinary catheter may cause haematuria in two
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52 453 other catheterized SVPE-treated patient taking oral aspirin, who had haematuria and sterile urine.
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3 454 We also monitored the major organ function and biochemical status of the patients treated with
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5 455 SVPE. No patients experienced hepatic or renal impairment. One patient developed anaemia and
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7 456 hypoalbuminemia; this patient had severe sepsis, a common cause of anaemia and
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9 457 hypoalbuminemia in critically ill patients admitted to an ICU (patient 11, Fig. 1). Electrolyte
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11 458 imbalances were detected in 15% of the SVPE-treated patients with GBS, and were mild,
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13 459 subclinical and easily corrected.

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18 461 The median reported durations to recovery of independent walking in patients with GBS in large-
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20 462 scale RCTs after PE are 53, 52 and 70 days^{4 5 7}; compared to 30 days in our patients treated with
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22 463 SVPE. Moreover, 60% of the patients with GBS treated with SVPE were able to walk
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24 464 independently at four weeks, whereas 20% of patients with GBS acquired independent walking
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26 465 ability at four weeks after traditional PE. However, these differences may possibly be due to the
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28 466 small sample size and variations in demographic and neurophysiological characteristics between
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30 467 cohorts. Finally, SVPE was completed in all 20 patients and no patients died.

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34 35 469 *Limitations of SVPE*

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37 470 SVPE is a time-consuming and labour-intensive procedure, which is a limitation. We used
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39 471 multiple thin-lumen tubing systems interconnected with a multichannel connector device, which
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41 472 may increase the chance of blood coagulating within the tubing system. Coagulation may require
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43 473 manipulation or replacement of the tubing to ensure free flow of blood and saline. Such handling
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45 474 could increase the chance of microbial contamination. A single continuous wide-lumen tubing
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47 475 system (SVPE kit) could resolve this problem. Most importantly, personnel conducting the SVPE
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49 476 procedure should maintain proper aseptic technique, which can sometimes be challenging in
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51 477 developing countries. Furthermore, other adaptations such as provision of a larger blood bag or
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3 478 increasing the number of days for SVPE could be considered to increase the plasma exchange
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5 479 rate.

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9 481 *Clinical implications and future research*

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11 482 Despite the limitations, our study showed SVPE is a safe and feasible treatment for GBS in a
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13 483 resource-limited setting where IVIg or PE are either unavailable or unaffordable. Specifically, the
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15 484 poorest 20% of the world's population (1.8 billion people) who typically earn less than 10 US\$
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17 485 per day and who are not covered by a national health insurance system may benefit. Considering
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19 486 the incidence of GBS is 2/100,000 in developing countries, approximately 40,000 patients could
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21 487 potentially benefit from SVPE every year, worldwide. In the future, a multicentre RCT is
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23 488 required to assess the clinical efficacy of SVPE for patients with GBS. If proven effective, SVPE
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25 489 could be an affordable and easily available alternative plasma exchange technique in low-income
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27 490 countries for patients with GBS and other disorders, who at present cannot afford standard PE
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29 491 due to its high cost and unavailability.

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3 500 **Declarations**
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26
27 510 size of the study. MV, MVJ, SR, and HPE contributed to the infection safety guidelines in the
28
29 511 study design. BI and QDM conducted the study and BI collected and analysed the data and
30
31 512 drafted the manuscript. All authors have critically revised the manuscript and have read and
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33 513 approved the final manuscript.
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11 527 comprised of an Ethical Review Committee (ERC) and Research Review Committee (RRC),
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13 528 reviewed and approved this study protocol on 09/12/2015 (reference number: PR-15086, version
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15 529 no 3).

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19 531 *Patient consent:* Obtained.

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23 533 *Data sharing:* The dataset is available from the lead author on request.

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27 535 *Transparency:* The corresponding author affirms that the manuscript is an honest, accurate and
28
29 536 transparent account of the study being reported; that no important aspects of the study have been
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31 537 omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have
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33 538 been explained.

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678 Table 1: Demographic and clinical characteristics of the 20 patients with GBS included in this
679 small volume plasma exchange (SVPE) study at entry

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Characteristic	Value
Demography	
Sex [males: females (ratio)]	13:7 (1.85)
Age (years) ¶	33 (18 - 55)
Body weight (kg) ¶	60 (50 - 72)
Antecedent events ‡ (total)	18 (90%)
Diarrhoea	10 (50%)
Respiratory infection	5 (25%)
Fever	3 (15%)
Days from antecedent events to weakness ¶	7 (3 - 30)
Days between onset of weakness to admission ¶	7 (2-12)
Neurological deficits at entry	
Weakness in arms and legs	20 (100%)
Cranial nerve deficits	12 (60%)
Decreased deep tendon reflexes	20 (100%)
Sensory involvement	5 (25%)
GBS disability score §	4 19 (95%)
	5 1 (5 %)
Severity of weakness (MRC sum-score) ¶	20 (0-29)
Autonomic dysfunction	11 (55%)

681 ¶ Median (range); † increased protein level (> 45 mg/dL) in combination with CSF cell count <
682 50/µL; CSF = cerebrospinal fluid; NCS = nerve conduction study; ‡ symptoms of an infection in
683 the four weeks preceding the onset of weakness; § GBS disability score (0 - 6) = 0: healthy state;
684 1: minor symptoms and capable of running; 2: able to walk 10 meters or more without assistance
685 but unable to run; 3: able to walk 10 meters across an open space with help; 4: bedridden or
686 chair-bound; 5: requiring assisted ventilation for at least part of the day; 6: dead.

687 Table 2: Treatment characteristics and complications associated with SVPE in the 20 patients
 688 with GBS

Characteristic/complication	Value
<i>Treatment characteristics</i>	
Number of sessions of SVPE per patient [¶]	30 (24 - 42)
Volume of plasma removed per patient [¶]	8.4 (6.3 – 9.6)
Plasma exchange rate (mL/kg) [¶]	140 (110-175)
Time between hospital admission and SVPE (days) [¶]	8 (5-10)
Time between onset of weakness and start of SVPE (days) [¶]	8 (5-10)
Need to stop SVPE due to poor hemodynamic tolerance	0/20 (0%)
Need for blood transfusion for anaemia	1/20 (5%)
Reduction of anticoagulant drug dose for bleeding	3/20 (15%)
Temporary withdrawal of antiplatelet drug for bleeding	4/20 (20%)
Increased anticoagulant drug dose to continue SVPE	1/20 (5%)
CVC blockade/replacement	0/20 (0%)
<i>Complications during SVPE</i>	
<i>Infection</i>	
Leukocytosis	7/20 (35%)
CLABSI [§]	6.25
VAP [§]	136.4
CAUTI [§]	40
Severe sepsis	1/20 (5%)
Antimicrobial agents used	6/20 (30%)
<i>Bleeding and coagulation</i>	
Bleeding from CVC insertion site	10/20 (50%)
Bleeding from mucosal area	3/20 (15%)
Prolonged BT (BT > 10 min)	0/20 (0%)
Prolonged CT (CT > 15 min)	0/20 (0%)
Prolonged PT (PT > 14 sec) [¶]	6/20 (30%) [15-19 sec]

Prolonged aPTT (aPTT > 40 sec) ¶	3/20 (15%) [51-240 sec]
<i>Other complications</i>	
Saline responsive hypotension	10/20 (50%)
Anaemia (Hb < 8 gm/L)	2/20 (10%)
Thrombocytopenia (PC < 1.5 lac/µL) ¶	6/20 (30%) [0.79-1.3 lac/µL]
Jaundice (serum bilirubin > 1.2 mg/dL)	0/20 (0%)
Renal impairment (serum creatinin > 1.2 mg/dL)	0/20 (0%)
Hyponatraemia (serum Na ⁺ < 135 mEq/L)	1/20 (5%) [126 mEq/L]
Hypokalaemia (serum K ⁺ < 3.5 mEq/L) ¶	3/20 (15%) [2.6-3.2 mEq/L]
Hypoalbuminemia (serum albumin > 35 gm/L) ¶	4/20 (20%) [26-32 gm/L]
Hypocalcaemia (serum Ca ⁺ < 2.2 mmol/L) ¶	3/20 (15%) [1.89-1.98 mmol/L]
Hypomagnesaemia (serum Mg ⁺ < 75 mEq/L) ¶	1/20 (5%) [73 mEq/L]
Hypersensitivity/transfusion reaction to FFP	4/20 (20%)

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690 ¶ Median (range); § rate per 1000 device days; CLABSI: central line-associated bloodstream

691 infection; VAP: ventilator-associated pneumonia; CAUTI: catheter-associated urinary tract

692 infection; CVC: central venous catheter; BT: bleeding time, CT: clotting time; PT: prothrombin

693 time; APTT: activated partial thromboplastin time; FFP: fresh frozen plasma.

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695 Table 3: Neurological outcomes of the 20 patients with GBS after SVPE
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Clinical outcome	1 month	2 months	3 months	6 months
Cranial nerve involvement	7/20 (35%)	6/20 (30%)	4/20 (20%)	2/20 (10%)
Autonomic involvement	3/20 (15%)	3/20 (15%)	0/20 (0%)	0/20 (0%)
Sensory dysfunction	1/20 (5%)	1/20 (5%)	1/20 (5%)	1/20 (5%)
GBS disability score [¶]	0 = 0	0 = 1	0 = 1	0 = 2
	1 = 3	1 = 6	1 = 7	1 = 7
	2 = 9	2 = 6	2 = 6	2 = 5
	3 = 2	3 = 1	3 = 1	3 = 3
	4 = 3	4 = 5	4 = 5	4 = 3
	5 = 3	5 = 1	5 = 0	5 = 0
MRC sum score [†] *	47 (0-60)	49 (0-60)	53 (6-60)	58 (22-60)
ONLS [‡] *	4 (1-12)	3 (0-12)	3 (0-12)	2 (0-10)
R-ODS [§] *	26 (0-41)	33 (0-45)	37 (0-45)	38 (0-46)

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698 * Median (range); ¶ GBS disability score (0 - 6) = 0: healthy state, 1: minor symptoms and

699 capable of running, 2: able to walk 10 meters or more without assistance but unable to run, 3:

700 able to walk 10 meters across an open space with help, 4: bedridden or chair-bound, 5: requiring

701 assisted ventilation for at least part of the day, 6: dead; † MRC sum score: Medical Research

702 Council sum score; ‡ ONLS: Overall Neuropathy Limitation Scale²²; § R-ODS: Rash-built

703 Overall Disability Score²³

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3 714 **Figure 1:** Feasibility of SVPE and associated complications for the 20 individual patients with
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5 715 GBS.

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9 717 SVPE: small volume plasma exchange, HAI: hospital acquired infection, V: ventilator-associated
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11 718 pneumonia, B: central line-associated blood stream infection, U: catheter-associated urinary tract
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13 719 infection, ^A measured in litres, ●: spell of hypotension (systolic BP < 90 mm Hg), ◊ : CVC
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15 720 insertion site bleeding, ▲: hypersensitivity to fresh frozen plasma, shaded squares: pyrexia due to
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17 721 bacterial infection, dotted squares: pyrexia due to suspected viral infection, M: onset of mechanical
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19 722 ventilation, C: urinary catheterization.

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26 725 **Figure 2:** Hospital-acquired infections and use of antibiotics in the 20 patients with GBS receiving
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28 726 SVPE compared to the 24 hospital control patients without GBS treated in an ICU with a CVC who
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30 727 did not receive SVPE.

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34 729 ■ SVPE ($n = 20$): twenty patients with GBS aged ≥ 18 -years-old who were bedbound (GBS
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36 730 disability score ≥ 4) received small volume plasma exchange (SVPE) within 2 weeks of the onset
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38 731 of weakness. □ Non-SVPE ($n=20$): twenty-four patients aged ≥ 18 -years-old with a diagnosis
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40 732 other than GBS who required a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU
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42 733 and HDU units in the same period as the patients with GBS received SVPE; * $p < 0.0001$.

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49 736 **Figure 3:** Kaplan-Meier estimate (with 95% confidence limits) of the cumulative incidence of
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51 737 restoration of independent walking ability in patients with GBS treated with SVPE.

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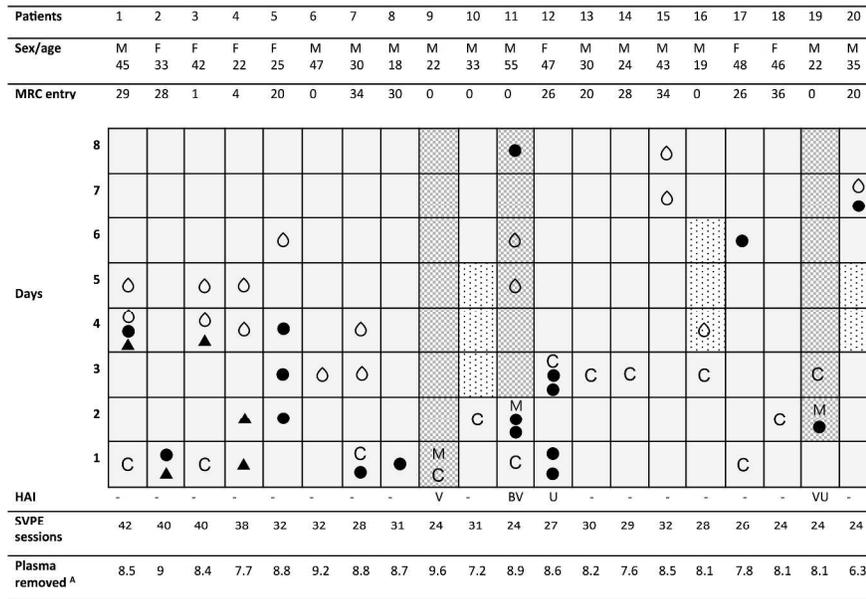


Figure 1: Feasibility of SVPE and associated complications for the 20 individual patients with GBS. SVPE: small volume plasma exchange, HAI: hospital acquired infection, V: ventilator-associated pneumonia, B: central line-associated blood stream infection, U: catheter-associated urinary tract infection, A measured in litres, black dot: spell of hypotension (systolic BP < 90 mm Hg), empty drop: CVC insertion site bleeding, black triangle: hypersensitivity to fresh frozen plasma, shaded squares: pyrexia due to bacterial infection, dotted squares: pyrexia due to suspected viral infection, M: onset of mechanical ventilation, C: urinary catheterization.

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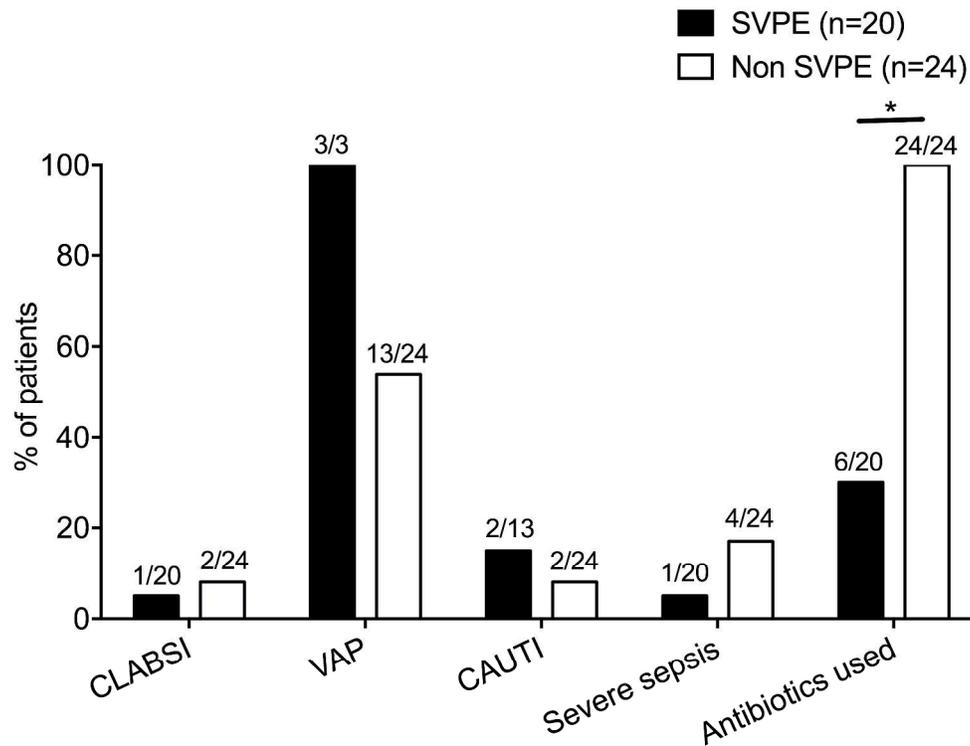


Figure 2: Hospital-acquired infections and use of antibiotics in the 20 patients with GBS receiving SVPE compared to the 24 hospital control patients without GBS treated in an ICU with a CVC who did not receive SVPE.

■ SVPE (n = 20): twenty patients with GBS aged ≥ 18 -years-old who were bedbound (GBS disability score ≥ 4) received small volume plasma exchange (SVPE) within 2 weeks of the onset of weakness. □ Non-SVPE (n=20): twenty-four patients aged ≥ 18 -years-old with a diagnosis other than GBS who required a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period as the patients with GBS received SVPE; * $p < 0.0001$.

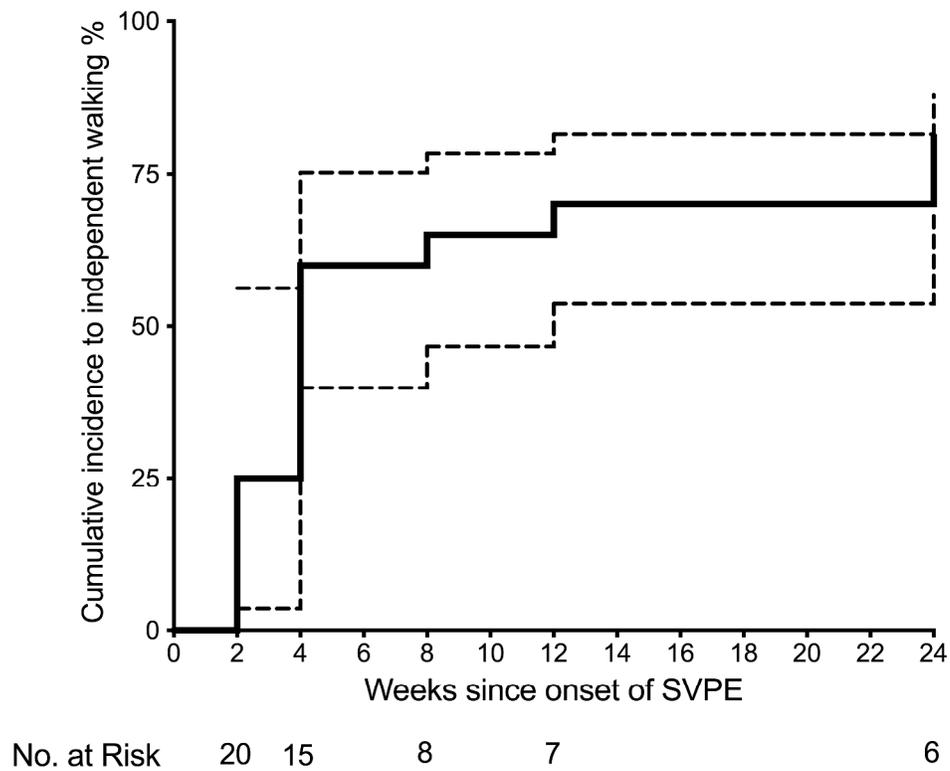
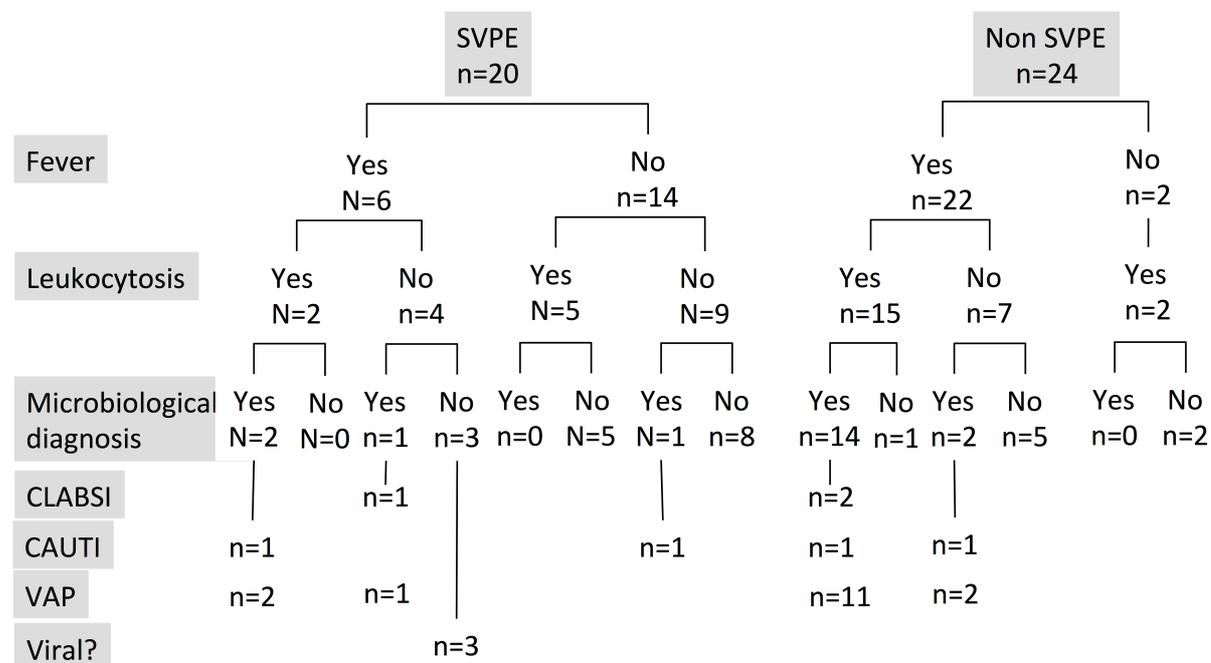


Figure 3: Kaplan-Meier estimate (with 95% confidence limits) of the cumulative incidence of restoration of independent walking ability in patients with GBS treated with SVPE.

Supplementary Figure: Hospital-acquired infections in the 20 patients with GBS treated with SVPE and the 24-hospital control patients without GBS.



SVPE: small volume plasma exchange, CLABSI: central line-associated blood stream infection, CAUTI: catheter-associated urinary tract infection, VAP: ventilator-associated pneumonia.

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2017 CONSORT checklist of information to include when reporting a randomized trial assessing nonpharmacologic treatments (NPTs)*.
Modifications of the extension appear in italics and blue.

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
Title and abstract					
	1a	Identification as a randomized trial in the title	NA (Non-randomized)		
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3, 4, 5	Refer to CONSORT extension for abstracts for NPT trials	3, 4, 5
Introduction					
Background and objectives	2a	Scientific background and explanation of rationale	6		
	2b	Specific objectives or hypotheses	6, 7		
Methods					
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7	When applicable, how care providers were allocated to each trial group	NA
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	No changes to methods after trial commencement		
Participants	4a	Eligibility criteria for participants	7, 8	When applicable, eligibility criteria for centers and for care providers	NA
	4b	Settings and locations where the data were collected	7		
Interventions†	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7, 8	Precise details of both the experimental treatment and comparator	7, 8
	5a			Description of the different components of the interventions and, when applicable, description of the procedure for tailoring the interventions to individual participants.	9
	5b			Details of whether and how the interventions were standardized.	8, 9

Cite as: Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40-7.

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
	5c.			Details of whether and how adherence of care providers to the protocol was assessed or enhanced	8, 9
	5d			Details of whether and how adherence of participants to interventions was assessed or enhanced	NA
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9		
	6b	Any changes to trial outcomes after the trial commenced, with reasons	No changes to trial outcomes after the trial commenced		
Sample size	7a	How sample size was determined	9	When applicable, details of whether and how the clustering by care providers or centers was addressed	NA
	7b	When applicable, explanation of any interim analyses and stopping guidelines	10		
Randomization:					
- Sequence generation	8a	Method used to generate the random allocation sequence	NA (Non-randomized)		
	8b	Type of randomization; details of any restriction (such as blocking and block size)	NA (Non-randomized)		
- Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	NA (Non-randomized)		
- Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	NA (Non-randomized)		
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Blinding was not possible	If done, who was blinded after assignment to interventions (e.g., participants, care providers, those administering co-interventions, those assessing outcomes) and how	Blinding was not possible

Cite as: Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40-7.

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
	11b	If relevant, description of the similarity of interventions	7, 8		
	11c			If blinding was not possible, description of any attempts to limit bias	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10	When applicable, details of whether and how the clustering by care providers or centers was addressed	NA
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA		
Results					
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	11	The number of care providers or centers performing the intervention in each group and the number of patients treated by each care provider or in each center	Single center study
	13b	For each group, losses and exclusions after randomization, together with reasons	No losses and exclusions after inclusion		
	13c			For each group, the delay between randomization and the initiation of the intervention	11
	new			Details of the experimental treatment and comparator as they were implemented	11-16
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7		
	14b	Why the trial ended or was stopped	NA (Trial completed)		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1	When applicable, a description of care providers (case volume, qualification, expertise, etc.) and centers (volume) in each group.	NA
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11-12		

Cite as: Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40-7.

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12-16		
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	15		
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12-15		
Discussion					
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	20-21	In addition, take into account the choice of the comparator, lack of or partial blinding, and unequal expertise of care providers or centers in each group	NA
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	16-20	Generalizability (external validity) of the trial findings according to the intervention, comparators, patients, and care providers and centers involved in the trial	16-20
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16-20		
Other information					
Registration	23	Registration number and name of trial registry	4		
Protocol	24	Where the full trial protocol can be accessed, if available	Manuscript reference no: 17		
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	22		

*Additions or modifications to the 2010 CONSORT checklist. CONSORT = Consolidated Standards of Reporting Trials

†The items 5, 5a, 5b, 5c, 5d are consistent with the Template for Intervention Description and Replication (TIDieR) checklist

Cite as: Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. *Annals of Internal Medicine*. 2017 Jul 4;167(1):40-7.

Table: Required documents of the safety and feasibility study of the small volume plasma exchange (SVPE) for Guillain-Barré syndrome patients for the World Health Organization Trial Registration Data Set

	Item/Label	Description
1	Primary Registry and Trial Identifying Number	Clinicaltrials.gov NCT02780570
2	Date of Registration in Primary Registry	May 23, 2016
3	Secondary Identifying Numbers	International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) Protocol Number: PR-15086, Version no. 3, Date: 09/12/2015
4	Source(s) of Monetary or Material Support	GBS/CIDP Foundation International Fondation Mérieux: (Small Grants Program 2015)
5	Primary Sponsor	GBS/CIDP Foundation International
6	Secondary Sponsor(s)	Fondation Mérieux: (Small Grants Program 2014)
7	Contact for public queries	MD. BADRUL ISLAM Email: bislamdmch@gmail.com Telephone no: +880 1712 89 0172 Postal address: Dr. Badrul Islam

		Research trainee and PhD Fellow Laboratory Sciences and Services Division (LSSD) Icddr,b Dhaka, Bangladesh
8	Contact for scientific queries	MD. BADRUL ISLAM Principal Investigator (PI) Email: bislamdmch@gmail.com Telephone no: +880 1712 89 0172 Postal address: Dr. Badrul Islam Research trainee and PhD Fellow Laboratory Sciences and Services Division (LSSD) Icddr,b Dhaka, Bangladesh
9	Public title	Small volume plasma exchange for Guillain-Barré syndrome
10	Scientific title	Small volume plasma exchange for Guillain-Barré syndrome in low-income countries: a safety and feasibility study
11	Countries of Recruitment	Bangladesh
12	Health condition(s) or problem(s) studied	Guillain-Barré syndrome (GBS)
13	Interventions	<u><i>Small Volume Plasma Exchange (SVPE)</i></u> A loading dose of low-molecular weight heparin (1.5 mg/kg) will be given subcutaneously at least two hours

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3 before initiation of SVPE; the same dose will be
4 administered once daily or divided into two equal doses
5 daily for eight days or until SVPE is completed. Whole
6 blood (7 mL/kg body weight) will be drawn from the
7 central venous catheter into the blood transfusion bag
8 in each session. The blood bag will be hung beside the
9 patient for 2.5 h on a saline stand and left
10 uninterrupted to allow plasma and blood cells to
11 separate. The blood cells will be infused back into the
12 patient and plasma will be discarded and replaced with
13 fresh frozen plasma and colloid solution alternately (in
14 equal volumes) via the closed-circuit SVPE kit illustrated
15 in. In case of excessive clotting (bleeding time reduction
16 of > 50% of baseline for that patient), aspirin (600 mg)
17 will be administered orally at least two hours before
18 the next SVPE session and continued thereafter at 150
19 mg orally/day until SVPE is completed. One blood bag
20 will be used each day, with a total of six sessions/day. A
21 total of 48 sessions will be performed over eight days,
22 removing approximately 8000 mL plasma in total.
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39 Central venous catheterized patients without GBS

40 To compare the safety of SVPE in patients with GBS in
41 the context of the background risk of central line-
42 associated blood stream infection (CLABSI) at the study
43 intensive care (ICU) and high-dependency care (HDU)
44 units, the incidence of CLABSI will be assessed in a
45 control group of adult patients with a diagnosis other
46 than GBS admitted to the same ICU and HDU units in
47 the same period of time the patients with GBS will be
48 enrolled for SVPE. We will assess the rate of CLABSI in
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		<p>patients aged ≥ 18-years-old requiring a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units.</p>
14	Key Inclusion and Exclusion Criteria	<p><u><i>Inclusion criteria for SVPE in GBS patients</i></u></p> <ol style="list-style-type: none"> 1. Patients aged ≥ 18-years-old fulfilling the diagnostic criteria for GBS of the National Institute of Neurological and Communicative Disorders and Stroke (NINDS) 2. Unable to walk unaided for more than 10 meters (GBS disability score ≥ 3) 3. Presented within 2 weeks of the onset of weakness 4. Unable to afford standard treatment with IVIg or PE. <p><u><i>Exclusion criteria for SVPE in GBS patients</i></u></p> <ol style="list-style-type: none"> 1. Patients with severe or terminal concomitant illness 2. Evidence of healthcare-associated infection on admission (except for aspiration pneumonia) 3. Previous history of severe allergic reaction to properly matched blood products and pregnant women will be excluded from the study. <p><u><i>Inclusion criteria for patients without GBS</i></u></p> <ol style="list-style-type: none"> 1. Patients aged ≥ 18-years-old 2. Requiring a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period of time the patients with GBS enrolled for SVPE. <p><u><i>Exclusion criteria for patients without GBS</i></u></p>

		<ol style="list-style-type: none"> 1. Patients with healthcare-associated infection present on admission (except aspiration pneumonia) 2. Pregnant women
15	Study type	<p><u>Type of the study:</u> Interventional</p> <p><u>Method of allocation:</u> Non-randomized</p> <p><u>Masking:</u> Non-masked</p> <p><u>Assignment:</u> Parallel arm</p> <ul style="list-style-type: none"> • SVPE in patients with GBS • Rate of CLABSI in patients without GBS <p><u>Purpose:</u> Safety and feasibility of SVPE</p>
16	Date of first enrolment	February 20, 2016
17	Target sample size	<p>SVPE in patients with GBS = 20</p> <p>Rate of CLABSI in patients without GBS = ≥ 20</p>
18	Recruitment status	<p>Completed:</p> <ul style="list-style-type: none"> • Twenty cases of GBS have been successfully treated with SVPE and 24 control cases without GBS have been recruited.
19	Primary Outcome(s)	<p><u>Primary outcome of safety:</u></p> <ol style="list-style-type: none"> 1. Number of patients with GBS treated with SVPE developing severe sepsis or septic shock due to central line associated blood stream infection (CLABSI) as per standard guideline (Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central line-associated Bloodstream Infection); CDC Device-associated Module, BSI. January 2017) 2. Occurrence of venous thrombosis in the limb

		<p>where the CVC is placed. Venous thrombosis will be assessed according to Wells criteria (Philip S. Wells et al. Evaluation of d -Dimer in the Diagnosis of Suspected Deep-Vein Thrombosis; N Engl J Med 2003;349:1227-35)</p> <p><u>Primary outcome of feasibility:</u></p> <ol style="list-style-type: none"> 1. Ability to remove at least eight litres of plasma by SVPE over eight days.
20	Secondary Outcome(s)	<p><u>Secondary outcome of safety:</u></p> <ol style="list-style-type: none"> 2. Relative risk of CLABSI due to SVPE compared to CLABSI in control patients without GBS treated using a CVC 3. Hemodynamic instability during the SVPE procedure (variations in systolic blood pressure greater than 30 mmHg or sudden bradycardia involving a reduction in heart rate by more than 20 beats per min within 30 min of starting SVPE or an increase in heart rate above 120 beats per min) 4. Development of anaemia (Hb <7 gm/dL) or serious haemorrhage requiring blood transfusion. <p><u>Secondary outcome of feasibility:</u></p> <ol style="list-style-type: none"> 1. Rate of CVC occlusion during the SVPE procedure 2. The healthcare personnel's acceptability and

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		<p>satisfaction with the SVPE procedure and any unanticipated events compromising the SVPE procedure as assessed using a standard questionnaire.</p> <p>3. Neurological outcome will be assessed in terms of improvement in GBS disability score and MRC sum score at discharge and up to 4 weeks after entry.</p>
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For peer review only

BMJ Open

Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings: a phase II safety and feasibility study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022862.R3
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Date Submitted by the Author:	08-Jun-2018
Complete List of Authors:	Islam, Md Badrul; International Centre for Diarrhoeal Disease Research Bangladesh, LSSD Islam, Zhahirul; The International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) , Laboratory Sciences and Services Division (LSSD) Rahman, Shafiqur; Uttara Adhunik Medical College, Anaesthesia and Intensive Care Endtz, Hubert; Erasmus University Medical Center, Department of Medical Microbiology and Infectious Diseases; Fondation Merieux Vos, Margreet; Erasmus MC Medical Center Rotterdam, Department of Medical Microbiology and Infectious diseases van der Jagt, Mathieu; Erasmus MC, Department of Intensive Care Van Doorn, Peter; Erasmus University Medical Center, Department of Neurology Jacobs, BC; Erasmus University Medical Center, Departments of Neurology and Immunology Mohammad, Quazi; National Institute of Neuroscience
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Medical management
Keywords:	Guillain-Barré syndrome, Small volume plasma exchange, Safety, Feasibility
<p>Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.</p> <p>SUPPLEMENTARY VIDEO.mp4</p>	

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5 2 Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings:
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7 3 a phase II safety and feasibility study
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51
52 48 Word count: 5087 (Excluding abstract, reference, table and figures)
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3 50 **ABSTRACT**

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5 51 **OBJECTIVE**

6
7 52 To assess the safety and feasibility of small volume plasma exchange (SVPE) for Guillain-Barré
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9 53 syndrome (GBS) patients.

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11 54 **DESIGN**

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14 55 Non-randomized, single arm, interventional trial.

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16 56 **SETTING**

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18 57 National Institute of Neurosciences and Hospital, Dhaka, Bangladesh.

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20 58 **PARTICIPANTS**

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22 59 Twenty adult (>18 years) patients with GBS presented within 2 weeks of onset of weakness who
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24 60 were unable to walk unaided for more than 10 meters.

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26 61 **INTERVENTIONS**

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29 62 SVPE involves blood cell sedimentation in a blood bag and removal of supernatant plasma after
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31 63 blood cells are re-transfused. This procedure was repeated three to six times a day, for eight
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33 64 consecutive days. Fresh frozen plasma (FFP) and normal saline were used as replacement fluid.

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35 65 **OUTCOME MEASURES**

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37 66 Serious adverse events (SAE) were defined as severe sepsis and deep venous thrombosis related
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39 67 to the central vein catheter (CVC) used during SVPE. SVPE was considered safe if less than 5/20
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41 68 patients experienced a SAE, and feasible if 8 L plasma could be removed within 8 days in at least
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43 69 15/20 patients.

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45 70 **RESULTS**

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48 71 Median patient age 33 years (IQR 23-46; range 18-55); 13 (65%) were male. Median MRC sum
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50 72 score was 20 (IQR 0-29; range 0-36); three (15%) patients required mechanical ventilation. One
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52 73 patient developed SAE (severe sepsis, possibly related to CVC). The median plasma volume
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54 74 exchanged was 140 mL/kg (range 110-175) and removal of 8 L plasma was possible in 15 (75%)

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3 75 patients. Patients received a median 1g/kg IgG via FFP although a substantial proportion of IgG
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5 76 was probably removed again by the SVPE sessions. GBS disability score improved by at least
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7 77 one grade in 14 (70%) patients four weeks after SVPE started. No patients died.
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9 78 CONCLUSION

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11 79 SVPE seems a safe and feasible alternative treatment to standard PE or IVIg for GBS; further
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13 80 studies of clinical efficacy in low-resource developing countries are warranted.
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18 82 TRIAL REGISTRATION

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20 83 Clinicaltrials.gov NCT02780570 on May 23, 2016
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3 92 **Strength and limitations of the study:**
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7 94 1. The strength of this study underlies the novel and simple technique of SVPE, which is
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9 95 much less expensive than conventional immunotherapies [plasma exchange (PE) and
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11 96 intravenous immunoglobulin (IVIg)]

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13 97 2. SVPE is corroborated as safe and feasible for the first time in a prospective and
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15 98 standardized cohort of patients with Guillain-Barré syndrome (GBS).

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18 99 3. The intrinsic limitations of this study are its non-randomized, single arm nature, which is
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20 100 conducted in a single center with a limited sample size of GBS patients. The volume
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22 101 exchanged was at the lower range compared to previous PE studies conducted in GBS.

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24 102 4. Clinical efficacy of SVPE on patients with GBS was a secondary end-point assessment
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26 103 and therefore deserves a randomized controlled trial in future to assess the clinical
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28 104 efficacy of SVPE for the patients with GBS.

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107 **Introduction**

108 Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy with a
109 yearly incidence of 1.2 to 2.3 cases per 100,000 per year.¹ GBS is characterized by rapidly
110 progressive limb weakness and, in a proportion of cases, respiratory failure (25%) or severe
111 autonomic dysfunction (10%). Plasma exchange (PE) was the first treatment proven to be
112 effective for GBS, if given within 4 weeks of the onset of weakness.²⁻¹¹ Conventionally for GBS
113 patients, three to five plasma exchange sessions are done in alternate days within a span of 7 to
114 14 days targeting a plasma exchange rate of 120 - 200 ml/kg (40-50ml/kg/day).⁷ Later studies
115 showed treatment with intravenous immunoglobulin (IVIg) (0.4 g/kg per day for 5 days) has a
116 similar efficacy as PE in patients with GBS who are unable to walk, if started within 2 weeks of
117 the onset of weakness.^{12 13}

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119 Unfortunately, most patients in low-income countries cannot afford expensive treatment with
120 either PE or IVIg.¹⁴ In Bangladesh, a full course of IVIg for a 60 kg adult costs approximately
121 12,000-16,000 US\$ and treatment with conventional PE for 5 days costs approximately 4,500-
122 5,000 US\$. The mean income in Bangladesh was 4 US\$ per day in 2016 (World Bank and
123 Bangladesh Bureau of Statistics 2016); IVIg and PE cost the equivalent of 3,000 and 1,250 mean
124 income days, respectively. At present, the majority (92%) of patients with GBS in Bangladesh
125 receive supportive care only.¹⁴ In addition, mobile PE equipment is not available in Bangladesh;
126 therefore, patients admitted to the intensive care unit (ICU) cannot receive PE. We previously
127 reported the mortality rates for GBS in Bangladesh range from 12 to 14% and observed 29% of
128 patients with GBS in Bangladesh are unable to walk at 6 months after onset; these poor outcomes
129 are undoubtedly due to the low rates of specific treatment with PE or IVIg.^{15 16}

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3 131 Small volume plasma exchange (SVPE) may represent a cheap, effective alternative treatment for
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5 132 GBS. SVPE is based on the same principle as conventional PE (selective removal of plasma) but
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7 133 uses a novel, simple technique with much lower costs (approximately 500 US\$). The current non-
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9 134 randomized trial was designed to investigate the safety and feasibility of SVPE in 20 patients
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11 135 with GBS admitted to the National Institute of Neurosciences Hospital in Dhaka, Bangladesh.
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15 16 137 **Methods/Design**

17 18 138 *Study design*

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20 139 For this non-randomized, single arm, interventional safety and feasibility trial, 20 adult patients
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22 140 with GBS were enrolled between March 2016 and December 2016 for SVPE at the National
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24 141 Institute of Neurosciences and Hospital (NINS), Dhaka, Bangladesh. A detailed study protocol
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26 142 was published previously and includes definitions of all variables used in this study.¹⁷
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31 144 Four to six daily sessions of whole blood sedimentation and removal of supernatant plasma after
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33 145 re-transfusion of the sedimented blood cells was planned for the 20 patients with GBS, with a
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35 146 target of removing an overall volume of at least 8 litres (L) of plasma over a total of 8 days.¹⁷
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37 147 (See supplementary video for SVPE procedure)
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42 149 Patients with GBS were monitored according to a standard protocol throughout the course of
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44 150 SVPE until the second day after withdrawal of the central venous catheter (CVC) in order to
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46 151 assess predefined measures of safety and feasibility and followed up for six months to assess
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48 152 neurological outcome. The protocol was reviewed and approved by the institutional research and
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50 153 ethics review committees at the icddr,b and registered at clinicaltrials.gov (NCT02780570).¹⁷ All
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52 154 patients provided written informed consent to participate in this study.
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3 156 *Patient and Public Involvement*
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5 157 Patients and or public were not involved either in the development of the research question, study
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7 158 design and outcome measure or recruitment to and conduct of the study.
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11 160 *Inclusion and exclusion criteria for patients with GBS*
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13 161 Patients aged ≥ 18 -years-old fulfilling the diagnostic criteria for GBS of the National Institute of
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15 162 Neurological and Communicative Disorders and Stroke (NINDS)¹⁸ were enrolled, provided they
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17 163 were unable to walk unaided for more than 10 meters (GBS disability score ≥ 3), presented
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19 164 within 2 weeks of the onset of weakness, and were unable to afford standard treatment with IVIg
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21 165 or PE. Patients with concomitant severe or terminal illnesses, evidence of healthcare-associated
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23 166 infection (HAI) on admission (except for aspiration pneumonia), a previous history of severe
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25 167 allergic reactions to properly matched blood products, and pregnant women were excluded from
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27 168 the study.
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33 170 *Control cohort*
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35 171 To compare the safety of SVPE in patients with GBS in the context of the background risk of
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37 172 central line-associated blood stream infection (CLABSI) at our institution, we prospectively
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39 173 assessed the incidence of CLABSI in a hospital control group of 24 adult patients without GBS
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41 174 receiving neurocritical care. Hospital controls were eligible based on the following
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43 175 characteristics: ≥ 18 -years-old, a neurological diagnosis other than GBS, and a CVC placed for $>$
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45 176 2 and ≤ 8 calendar days after admission to the same ICU or HDU unit as the SVPE-treated
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47 177 patients. Patients with a HAI (except aspiration pneumonia) and pregnant women were excluded
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49 178 from the control group.
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3 181 *Primary and secondary outcome measures*

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5 182 The primary outcome measures of safety were the number of patients with GBS treated with
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7 183 SVPE who developed either severe sepsis or septic shock due to CLABSI¹⁹ and the occurrence of
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9 184 venous thrombosis in the limb where the CVC was placed. The primary outcome measure of
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11 185 feasibility was the ability to remove at least 8 L of plasma over 8 days.

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13 186 The secondary outcome measures of the safety of SVPE were the relative risk of CLABSI due to
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15 187 SVPE (compared to CLABSI in the hospital control group without GBS), hemodynamic
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17 188 instability during the SVPE procedure, and development of anaemia (Hb < 8 gm/dL) or any
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19 189 catheter-related haemorrhage requiring a blood transfusion.

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21 190 The secondary outcome measure of feasibility of SVPE was the rate of CVC occlusion during the
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23 191 SVPE procedure. In addition, neurological outcome was assessed using the GBS disability
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25 192 score²⁰, MRC sum score²¹, Overall Neuropathy Limitation Scale (ONLS)²² and Rasch-built
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27 193 Overall Disability Scale (R-ODS)²³ at 1st, 2nd, 3rd, and 6th months from the start of SVPE.

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33 195 *Procedure safety documentation and cost of SVPE*

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35 196 Strict aseptic procedures were followed to prevent CLABSI.²⁴⁻²⁶ SVPE was documented in terms
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37 197 of the duration and amount of plasma removed in each session, and the type and volume of
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39 198 replacement fluid and fresh frozen plasma (FFP) used. Throughout the procedure, the
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41 199 haemodynamic, haematological, biochemical, coagulation and infection profiles of the SVPE-
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43 200 treated patients were monitored according to the protocol.¹⁷ Screening for hepatitis B and C
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45 201 viruses, human immunodeficiency virus (HIV) and syphilis were performed as patient baseline
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47 202 assessments, and also on donor FFP before administration. CLABSI, primary and secondary
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49 203 bloodstream infections¹⁹, catheter-associated urinary tract infection (CAUTI)²⁷, ventilator-
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51 204 associated pneumonia (VAP)²⁸ and other HAI^{29 30} were documented in the SVPE-treated patients
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53 205 with GBS and the hospital control group. Expenditure for the full course of SVPE will be
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3 206 approximately 500 US\$ [fresh frozen plasma (24 bags) = 240 US\$, blood bag and saline sets: 40
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5 207 US\$, low molecular weight heparin: 110 US\$, routine investigation: 50 US\$, saline: 10 US\$, CV
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7 208 catheter: 40 US\$ = total 490 US\$].
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11 210 *Sample size*

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13 211 This safety and feasibility study enrolled 20 patients with GBS for SVPE. We could not
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15 212 perform a formal power calculation for this safety and feasibility study. The sample size
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17 213 was based on previous pilot studies conducted in GBS.^{31 32} The baseline rate of CLABSI
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19 214 was measured in the hospital control group of 24 patients without GBS admitted to the
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21 215 same study facility who required a CVC for at least 8 days during the study period.
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25 217 *Stopping rules for the trial based on safety and feasibility*

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27 218 Decision to stop the SVPE trial was designated using a Bayesian approach.³³⁻³⁵
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29 219 Accordingly, a predictive success rate of 75% was predefined for the SVPE procedure. If
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31 220 more than 5 of 20 patients experienced an SAE, or if it appeared impossible to remove at
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33 221 least 8 L of plasma over 8 days in at least 15 of 20 patients, the procedure was considered
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35 222 unsafe or unfeasible.
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39 224 *Statistical analysis*

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42 225 The rate of HAIs (CLABSI, VAP and CAUTI) per 1000 device days were calculated by
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44 226 dividing the number of each HAI during the study period by the number of device days and
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46 227 multiplying the result by 1000. The infection safety profile for SVPE was assessed by
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48 228 calculating the standardized infection ratio to define the risk of HAIs in patients with GBS
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50 229 treated with SVPE. The standardised infection ratio (SIR) was calculated by dividing the
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52 230 number of observed HAI by the number of HAI predicted (i.e., the infection rate in the control
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231 group). The predicted HAI rate was calculated using the rates of HAI in the hospital control
232 group of patients without GBS during the study period. Percentage values were compared using
233 the Chi-square test or Fisher's exact test (two-tailed) and median values, the Mann-Whitney U-
234 test using SPSS 22 software (IBM SPSS Statistics for Windows Version 22.0., IBM Corp.,
235 Armonk, NY, USA). Analyses were performed on an intention-to treat basis. All *P*-values
236 reported are two-sided; $p < 0.05$ was considered significant.

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238 **Results**

239 *Patients and hospital controls*

240 The demographic and clinical characteristics of the 20 patients with GBS are given in Table 1.
241 The median age of the patients with GBS was 33 years (range; 18-55); median body weight was
242 60 kg (IQR, 55-65 kg; range, 50-72 kg) and 13 (65%) patients were male (Fig. 1). On admission
243 and before the start of SVPE, all 20 patients with GBS were unable to walk independently (GBS
244 disability score, 4). One patient required mechanical ventilation from the second day after the
245 onset of weakness; SVPE was started on the fourth day of mechanical ventilation (patient 9, Fig.
246 1). Two of the 19 patients who did not require mechanical ventilation at the start of the study
247 required mechanical ventilation on the second day after initiation of SVPE (patients 11 and 19,
248 11 and 2 days after the onset of weakness, respectively; Fig. 1). The median MRC sum score for
249 the limb muscles in all 20 patients was 20 (IQR: 0-29; range: 0-36; Fig. 1). Symptoms of a
250 preceding infection in the 4 weeks before the onset of weakness were present in 18 (90%)
251 patients with GBS, of whom 10 (50%) had diarrhoea. Median duration from admission to start of
252 SVPE was two days (IQR, 2-3 days; range, 0-7 days). Median duration to nadir from the onset of
253 weakness was five days (range, 1-13 days). Electrodiagnostic nerve conduction studies indicated
254 15 (75%) patients had an axonal subtype and 5 (25%) patients had a demyelinating subtype of
255 GBS. Median duration from onset of weakness to NCS examination was 10 days (range, 4-16

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3 256 days). All patients had albuminocytologic dissociation; median CSF protein was 166 mg/dL
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5 257 (range 117-253 mg/dL). Median duration from onset of weakness to CSF examination was 11
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7 258 days (range, 4-17 days).

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11 260 Median age of the 24 hospital control patients without GBS was 44 years (IQR, 25-57; range; 18-
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13 261 74); 10 (42%) were male. Age and gender distribution were not significantly different compared
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15 262 to the 20 patients with GBS ($p = 0.2155$, $p = 0.1434$, respectively). The diagnoses for these 24
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17 263 patients were: brain tumour ($n = 5$), transverse myelitis ($n = 5$), head trauma after road traffic
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19 264 accident ($n = 3$), viral meningoencephalitis ($n = 2$), myasthenia gravis ($n = 2$), compressive
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21 265 cervical myelopathy ($n = 2$), cerebrovascular accident ($n = 2$), motor neuron disease ($n = 1$),
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23 266 electrolyte imbalance ($n = 1$) and status epilepticus ($n = 1$).

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27 28 29 268 *Primary endpoints*

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31 269 One patient with GBS treated with SVPE developed severe sepsis, possibly due to SVPE-related
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33 270 CLABSI (SVPE window-period blood culture revealed methicillin-resistant *Staphylococcus*
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35 271 *aureus*). This patient required intravenous fluid, noradrenalin infusion and intravenous
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37 272 antibiotics, but eventually improved (patient 11, Fig. 1). This patient also had signs and
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39 273 symptoms suggestive of aspiration pneumonia and VAP; *Streptococcus spp.* was isolated from
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41 274 pulmonary aspirates. Further laboratory results revealed dys-electrolytemia, anaemia and hypo-
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43 275 albuminemia. No patients experienced deep vein thrombosis due to the CVC for SVPE. Fifteen
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45 276 (75%) of the 20 patients met the primary endpoint of feasibility, defined as the ability to remove
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47 277 at least 8 L of plasma in eight days. The median volume of plasma removed was 8.5 L (IQR, 7.9-
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49 278 8.8 L; range, 6.3-9.6 L; Fig. 1). The median plasma exchange rate was 140 mL/kg bodyweight
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51 279 (IQR, 125-155 mL/kg; range, 110-175 mL/kg) over 8 days and 16 (80%) patients had a plasma
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53 280 exchange rate > 120 mL/kg (Table 2).

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3 281 *Secondary endpoints*

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5 282 *Infections among SVPE-treated patients with GBS and hospital controls*

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7 283 Among the 20 patients with GBS treated with SVPE, six (30%) had fever during SVPE (Fig. 1,
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9 284 Supplementary Figure 1), including 2 (10%) patients with leucocytosis who were diagnosed with
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11 285 HAI (VAP and CAUTI in one patient; VAP in one patient). In three out of four (20%) patients
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13 286 with fever without leucocytosis, fever subsided within two to three days without antimicrobial
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15 287 therapy (Fig. 1). The remaining patient with pyrexia without leucocytosis had microbiological
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17 288 evidence of both CLABSI and VAP (patient 11, Fig. 1). In all other 14 patients with GBS, no
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19 289 fever was documented during the course of SVPE until the tenth day of SVPE (second day after
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21 290 removal of the CVC for SVPE). Five of these 14 patients had leucocytosis, but no site-specific
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23 291 HAI could be detected. However, one of the nine patients without fever but leucocytosis fulfilled
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25 292 the criteria for CAUTI (patient 12, Fig. 1). All three patients who required mechanical ventilation
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27 293 subsequently developed VAP; two of the 13 patients who required a urinary catheter developed a
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29 294 CAUTI (patient 11, Fig. 1). No patients died during the 6 months follow-up.

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35 296 All 24-hospital control patients without GBS required mechanical ventilation and an indwelling
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37 297 urinary catheter. Of these patients, 22 (92%) patients had fever, of whom 15 (63%) had
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39 298 leucocytosis; a diagnosis of a specific HAI could be made 14 of these 15 patients (CLABSI in
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41 299 two, CAUTI in one, VAP in 11) and four (17%) fulfilled the criteria for severe sepsis
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43 300 (Supplementary Figure 1). Seven (29%) of the 24 hospital control patients had fever without
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45 301 leucocytosis. In two of these seven patients, a specific HAI was diagnosed (CAUTI and VAP in
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47 302 one, and VAP in one). In two hospital control patients, no fever was documented until day 10
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49 303 after first placement of the CVC, but leucocytosis was present and no site-specific HAI could be
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51 304 detected (Supplementary Figure 1).

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3 306 The rates of CLABSI, CAUTI and VAP per 1000 device days in the SVPE-treated patients with
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5 307 GBS were 6.25, 19.2 and 40 compared to 10.4, 10.4 and 67.7 for the hospital control patients
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7 308 without GBS, respectively. The relative risks of CLABSI, CAUTI and VAP associated with
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9 309 SVPE were 0.6, 1.2 and 1.8, respectively, compared to hospital control patients. The rates of
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11 310 CLABSI, CAUTI and VAP were comparable between SVPE-treated patients with GBS and
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13 311 hospital control patients ($p > 0.05$). Antimicrobial agents were used more frequently in the
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15 312 hospital control patients ($p < 0.0001$; Fig. 2). The standardised infection ratios for CLABSI,
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17 313 CAUTI and VAP for SVPE-treated patients with GBS were 0.6, 1.8 and 1.9, respectively.
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21 315 *Other secondary endpoints*

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24 316 Ten (50%) of the 20 patients treated with SVPE experienced transient hypotension during SVPE,
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26 317 which was corrected by infusion of 200-300 mL crystalloid saline (Fig. 1). Minor bleeding
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28 318 through the CVC insertion site (excluding at the time of insertion) was observed in 10/20 patients
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30 319 (50%; Fig. 1); these bleeds required a pressure pack. Reduction of the anticoagulant dose along
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32 320 with a pressure pack was required in 3/20 patients, who all had a prolonged prothrombin time
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34 321 (PT). Three patients had single episode of haemorrhage through the urinary catheter: one was
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36 322 diagnosed with a CAUTI with normal coagulation profile, one had a prolonged PT, the other had
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38 323 sterile haematuria with normal PT. Overall, PT and activated partial thromboplastin time (aPTT)
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40 324 were prolonged in 4/20 patients and only PT was prolonged in 2/20 patients. Clotting time and
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42 325 bleeding time were not prolonged in any patient. One patient developed anaemia (haemoglobin, 8
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44 326 gm/L) at the end of SVPE; this patient also had severe sepsis and required one unit of blood
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46 327 transfusion (patient 11, Fig. 1). CVC blockages were not observed in any SVPE-treated patients
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48 328 with GBS. One patient with increased clotting tendency who required an increased dose of low
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50 329 molecular weight heparin had shortened clotting time (CT) ($< 50\%$ of upper limit of normal),
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52 330 though PT was normal (patient 10, Fig. 1).
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3 331 The neurological outcomes of the SVPE-treated patients with GBS at six months in terms of
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5 332 neurological scores are given in Table 3. Median time to recover the ability to walk unaided was
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7 333 4 weeks (Fig. 3). Fourteen (70%) of the 20 patients had an improvement in GBS disability score
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9 334 of one or more grades at four weeks after the onset of SVPE. At one month, 12 patients (60%)
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11 335 were able to walk unaided, two patients (10%) were able to walk aided and six (30%) patients
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13 336 were bedbound, of whom three still required mechanical ventilation. At three months, 14 (70%)
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15 337 patients were able to walk unaided, one (5%) could walk with aid and five (25%) patients were
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17 338 bedbound. At six months, 14 (70%) patients were able to walk unaided, three (5%) could walk
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19 339 with aid and three (15%) remained bedbound (Table 3).
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25 341 *Other relevant clinical and laboratory findings*

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27 342 Allergic/transfusion reaction to FFP was observed in four patients with GBS treated with SVPE
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29 343 (Fig. 1). These transfusion reactions presented as an itchy erythematous skin rash (three patients),
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31 344 fever (two patients), hypotension (one patient) following transfusion of FFP; all of these reactions
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33 345 were managed with oral antihistamine (and intravenous saline in one patient) without further
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35 346 complications.
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40 348 The other documented haematological and biochemical abnormalities were hypo-albuminemia (n
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42 349 = 4), thrombocytopenia ($n = 6$), hyponatraemia ($n = 1$), hypokalaemia ($n = 3$), hypomagnesaemia
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44 350 ($n = 1$), hypocalcaemia ($n = 3$); (Table 2).
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49 352 *Immunoglobulin dosage admitted by FFP*

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51 353 During SVPE the median volume of FFP administered per GBS patient as replacement fluid was
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53 354 6000 ml (range, 5000 ml to 6000 ml). Considering the normal plasma IgG level of 11.20 mg/ml
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3 355 (range, 6.9 mg – 17.6 mg)³⁶, SVPE treated GBS patients received IgG dose of median 0.9 g/kg
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5 356 (range 0.6 g/kg – 1.3 g/kg).

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8 9 358 **Discussion**

10 11 359 *Principal findings*

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13 360 This study suggests SVPE may represent a safe and feasible alternative to conventional plasma
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15 361 exchange for patients with severe GBS in limited-resource settings. Of the 20 patients in this
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17 362 study, one (5%) experienced a SAE (severe sepsis due to probable CLABSI). The rate of SAE
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19 363 was not significantly higher than the hospital control group without GBS with a CVC, and no
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21 364 patients had a CVC-related thromboembolic event in patients with SVPE. We were able to
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23 365 remove the prespecified target volume (8 L) of plasma as the target primary endpoint of
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25 366 feasibility in 15/20 (75%) patients with GBS. Median plasma exchange volume and rate during
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27 367 SVPE were 8.4 L and 140 mL/kg, respectively. Minor adverse effects included transient
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29 368 hypotension during SVPE in 50% (10/20), minor haemorrhage from CVC insertion site in 50%
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31 369 (10/20), transfusion reaction to FFP in 20% (4/20), and hypo-albuminemia, anaemia and
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33 370 electrolyte imbalance in 20% (4/20) of patients. An improvement of at least one grade on the
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35 371 GBS disability score was observed for 14/20 (70%) patients at four weeks after the initiation of
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37 372 SVPE. No patients died.

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42 43 374 *Comparison with baseline hospital control patients and standard/modified PE*

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45 375 With respect to HAIs, no significant differences were observed in the frequency of CLABSI,
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47 376 severe sepsis, VAP or CAUTI between the SVPE-treated patients with GBS and 24 hospital
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49 377 control patients without GBS treated using a CVC in the same ICU or HDU (Fig. 2). However,
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51 378 antimicrobial agents were used more frequently, usually prophylactically, in the hospital control
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53 379 patients compared to the patients with GBS treated with SVPE ($p < 0.0001$; Fig. 2). The

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3 380 probability of detecting microorganisms in clinical infections may have been reduced due to
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5 381 overzealous use of antibiotics in the hospital control patients. Early trials of PE in patients with
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7 382 GBS showed 34% of patients develop severe infections.^{7 11} Subsequently, another large trial
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9 383 documented septicaemia in 19% of patients.⁵ However, the rates of CLABSI were not reported.
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13 385 A previous RCT on GBS from the US showed a beneficial effect with PE rate of 40-50
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15 386 ml/kg/session, for 3 to 5 sessions in 7 to 14 days, which comes to a total PE volume of 120-250
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17 387 ml/kg.⁷ The first French RCT on adult GBS patients showed beneficial effect of 4 PE sessions [2
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19 388 plasma volume (3.5 L) per PE session] over 8 days and in range, 6 – 12 L plasma was removed
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21 389 per patient.⁴ Subsequent French RCT with PE dose escalation showed, 2 PE sessions [1.5 plasma
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23 390 volume per PE session] are beneficial in mild to moderate GBS cases but less effective than 4 PE
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25 391 sessions in severe GBS cases and 6 PE sessions are as effective as 4 PE sessions in severe cases
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27 392 of GBS.⁵ In this RCT the exact total plasma volume exchanged per patient was not mentioned,
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29 393 but the authors indicated that the rate of plasma exchange was 40-ml/kg body weight per PE
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31 394 session. As to that a 60-70 kg person should have an exchange of 2.4 L-2.8 L per session and the
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33 395 therapeutic range of plasma volume to be exchanged would be 5.6 L to 11.2 L ml (2 to 4 PE
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35 396 sessions).
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39 398 During the piloting of the SVPE procedure we assessed that removal of 1 L of patient plasma
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41 399 could be feasible in a day. Therefore we defined our target plasma volume of 8 L to be removed
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43 400 in 8 days. The median total PE volume and rate in SVPE was 8.4 L and 140 ml/kg, which is at
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45 401 the lower range as compared to both the French and American RCT on PE for adult GBS
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47 402 patients. We were able to remove >120 mL/kg plasma in 80% of patients, which should provide a
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49 403 therapeutic effect.³⁷ Notably, the body weight of our patients may be lower than that of patients
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3 404 in western countries. In addition, SVPE was complete within 8 days, shorter than the usual time
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5 405 required for a full session of PE (10 to 12 days).

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7 406 Replacement fluid used in SVPE was FFP. We have several justifications in favour of using FFP
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9 407 instead of human albumin or other available colloidal solutions available in Bangladesh. First
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11 408 FFP is safe in terms of microbiological safety since stringent screening for viral and bacterial
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13 409 contamination was performed before infusion. Second, in contrast to human albumin and colloid
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15 410 solutions, FFP contains normal human IgG that could contribute to the beneficial
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17 411 immunotherapeutic effect in GBS. FFP was previously used as replacement fluid in large PE
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19 412 trials, quintessentially with the same volume (half the volume of replacement fluid) we used in
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21 413 SVPE.^{4,5} SVPE treated GBS patients received approximately half the amount of IgG from the
22
23 414 FFP used as replacement fluid compared to the total IVIg doses traditionally used in GBS
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25 415 (2gm/kg). Third, FFP contains all human plasma proteins that helps preservation of plasma
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27 416 colloid osmotic pressure and prevents formation of oedema and hypotension. Lastly FFP is much
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29 417 cheaper than commercial human albumin.
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35 419 In each day three units of FFP were transfused as replacement fluid after the last session of SVPE
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37 420 and in the initial two to three sessions, normal saline was used as replacement fluid. This was
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39 421 done to achieve the maximum immunotherapeutic effect of FFP as SVPE was not resumed before
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41 422 the next day and the IgG in FFP remained in the circulation overnight for a longer period of time
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43 423 (10 to 12 hours). However due to long half life of IgG, a substantial amount of IgG present in
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45 424 FFP were probably washed away due to repeated plasma removal both during SVPE and by
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47 425 conducting standard PE.
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52 427 In GBS, treatment with modified methods of PE done previously, were device based and done on
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54 428 limited number of GBS patients. In one study on 25 GBS patients from India, daily removal of
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3 429 small volume of plasma (10-15 ml plasma/kg body weight) for duration of median 3 days using
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5 430 traditional PE machine was shown to be clinically beneficial.³⁸ In another study from the same
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7 431 country, 12 GBS patients were treated with PE over 10 days using different PE-machine kit
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9 432 (REF627 kit from Haemonetics Corporation Limited on MCS+ machine) where authors claimed
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11 433 clinical improvement, however the main focus was on cost effectiveness and the total plasma
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13 434 volume exchanged per patient was not mentioned.³⁹ Nevertheless these methods are based on
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15 435 specific devices those are not in common practice, nor the trained personnel for these are
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17 436 available in the developing countries.
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22 438 Important observations in terms of secondary endpoints were transient hypotension, transfusion
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24 439 reaction to FFP and minor bleeding through the CVC insertion site. Hypotension is a common
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26 440 complication during traditional PE that affects nearly half of patients.⁵ Spells of hypotension
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28 441 during SVPE were more frequent during the three to four days after initiation of SVPE, and could
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30 442 be easily corrected by rapid infusion of 300-400 mL saline (Fig. 1). The hypotension could
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32 443 possibly be explained by hypovolemia due to drawing blood or as a result of the compromised
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34 444 autonomic nervous system in patients with GBS. As SVPE proceeded, hypotensive spells were
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36 445 encountered less frequently despite drawing the same volume of blood, which may in part be
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38 446 explained by adaptation of the vasomotor system or recovery from autonomic dysfunction. Minor
39
40 447 bleeding through the CVC insertion site occurred in 50% of patients and could be controlled by
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42 448 applying a simple pressure pack over the CVC insertion site in most cases; mild prolonged PT
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44 449 was noted in 30% (3/10) patients. However, spontaneous bleeding usually occurs if the PT is
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46 450 more than 2.5 times prolonged and PC is < 0.50 lac/ μ L.⁴⁰ Movement of the limb where the CVC
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48 451 was placed may have caused traction on the CVC and contributed to local bleeding in the other
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50 452 seven patients. Haematuria is not uncommon in patients with a UTI, as may have occurred in one
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52 453 SVPE treated patient; traumatic traction of the urinary catheter may cause haematuria in two
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3 454 other catheterized SVPE-treated patient taking oral aspirin, who had haematuria and sterile urine.
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5 455 We also monitored the major organ function and biochemical status of the patients treated with
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7 456 SVPE. No patients experienced hepatic or renal impairment. One patient developed anaemia and
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9 457 hypoalbuminemia; this patient had severe sepsis, a common cause of anaemia and
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11 458 hypoalbuminemia in critically ill patients admitted to an ICU (patient 11, Fig. 1). Electrolyte
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13 459 imbalances were detected in 15% of the SVPE-treated patients with GBS, and were mild,
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15 460 subclinical and easily corrected.
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20 462 The median reported durations to recovery of independent walking in patients with GBS in large-
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22 463 scale RCTs after PE are 53, 52 and 70 days^{4 5 7}; compared to 30 days in our patients treated with
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24 464 SVPE. Moreover, 60% of the patients with GBS treated with SVPE were able to walk
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26 465 independently at four weeks, whereas 20% of patients with GBS acquired independent walking
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28 466 ability at four weeks after traditional PE. However, these differences may possibly be due to the
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30 467 small sample size and variations in demographic and neurophysiological characteristics between
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32 468 cohorts. Finally, SVPE was completed in all 20 patients and no patients died.
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37 470 *Limitations of SVPE*

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39 471 SVPE is a time-consuming and labour-intensive procedure, which is a limitation. We used
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41 472 multiple thin-lumen tubing systems interconnected with a multichannel connector device, which
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43 473 may increase the chance of blood coagulating within the tubing system. Coagulation may require
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45 474 manipulation or replacement of the tubing to ensure free flow of blood and saline. Such handling
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47 475 could increase the chance of microbial contamination. A single continuous wide-lumen tubing
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49 476 system (SVPE kit) could resolve this problem. Most importantly, personnel conducting the SVPE
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51 477 procedure should maintain proper aseptic technique, which can sometimes be challenging in
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53 478 developing countries. Furthermore, other adaptations such as provision of a larger blood bag or
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3 479 increasing the number of days for SVPE could be considered to increase the plasma exchange
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5 480 rate.

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9 482 *Clinical implications and future research*

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11 483 Despite the limitations, our study showed SVPE is a safe and feasible treatment for GBS in a
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13 484 resource-limited setting where IVIg or PE are either unavailable or unaffordable. Specifically, the
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15 485 poorest 20% of the world's population (1.8 billion people) who typically earn less than 10 US\$
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17 486 per day and who are not covered by a national health insurance system may benefit. Considering
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19 487 the incidence of GBS is 2/100,000 in developing countries, approximately 40,000 patients could
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21 488 potentially benefit from SVPE every year, worldwide. In the future, a multicentre RCT is
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23 489 required to assess the clinical efficacy of SVPE for patients with GBS. If proven effective, SVPE
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25 490 could be an affordable and easily available alternative plasma exchange technique in low-income
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27 491 countries for patients with GBS and other disorders, who at present cannot afford standard PE
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29 492 due to its high cost and unavailability.

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3 501 **Declarations**
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26
27 511 size of the study. MV, MVJ, SR, and HPE contributed to the infection safety guidelines in the
28
29 512 study design. BI and QDM conducted the study and BI collected and analysed the data and
30
31 513 drafted the manuscript. All authors have critically revised the manuscript and have read and
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33 514 approved the final manuscript.
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15 530 no 3).
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20 532 *Patient consent:* Obtained.
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24 534 *Data sharing:* Extra data can be accessed via the Dryad data repository at <http://datadryad.org/>
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26 535 with the doi: 10.5061/dryad.55nb389
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31 537 *Transparency:* The corresponding author affirms that the manuscript is an honest, accurate and
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33 538 transparent account of the study being reported; that no important aspects of the study have been
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35 539 omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have
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37 540 been explained.
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680 Table 1: Demographic and clinical characteristics of the 20 patients with GBS included in this
681 small volume plasma exchange (SVPE) study at entry

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Characteristic	Value
Demography	
Sex [males: females (ratio)]	13:7 (1.85)
Age (years) ¶	33 (18 - 55)
Body weight (kg) ¶	60 (50 - 72)
Antecedent events ‡ (total)	18 (90%)
Diarrhoea	10 (50%)
Respiratory infection	5 (25%)
Fever	3 (15%)
Days from antecedent events to weakness ¶	7 (3 - 30)
Days between onset of weakness to admission ¶	7 (2-12)
Neurological deficits at entry	
Weakness in arms and legs	20 (100%)
Cranial nerve deficits	12 (60%)
Decreased deep tendon reflexes	20 (100%)
Sensory involvement	5 (25%)
GBS disability score §	4 19 (95%)
	5 1 (5 %)
Severity of weakness (MRC sum-score) ¶	20 (0-29)
Autonomic dysfunction	11 (55%)

683 ¶ Median (range); † increased protein level (> 45 mg/dL) in combination with CSF cell count <
684 50/µL; CSF = cerebrospinal fluid; NCS = nerve conduction study; ‡ symptoms of an infection in
685 the four weeks preceding the onset of weakness; § GBS disability score (0 - 6) = 0: healthy state;
686 1: minor symptoms and capable of running; 2: able to walk 10 meters or more without assistance
687 but unable to run; 3: able to walk 10 meters across an open space with help; 4: bedridden or
688 chair-bound; 5: requiring assisted ventilation for at least part of the day; 6: dead.

689 Table 2: Treatment characteristics and complications associated with SVPE in the 20 patients
690 with GBS

Characteristic/complication	Value
<i>Treatment characteristics</i>	
Number of sessions of SVPE per patient [¶]	30 (24 - 42)
Volume of plasma removed per patient [¶]	8.4 (6.3 – 9.6)
Plasma exchange rate (mL/kg) [¶]	140 (110-175)
Time between hospital admission and SVPE (days) [¶]	8 (5-10)
Time between onset of weakness and start of SVPE (days) [¶]	8 (5-10)
Need to stop SVPE due to poor hemodynamic tolerance	0/20 (0%)
Need for blood transfusion for anaemia	1/20 (5%)
Reduction of anticoagulant drug dose for bleeding	3/20 (15%)
Temporary withdrawal of antiplatelet drug for bleeding	4/20 (20%)
Increased anticoagulant drug dose to continue SVPE	1/20 (5%)
CVC blockade/replacement	0/20 (0%)
<i>Complications during SVPE</i>	
<i>Infection</i>	
Leukocytosis	7/20 (35%)
CLABSI [§]	6.25
VAP [§]	136.4
CAUTI [§]	40
Severe sepsis	1/20 (5%)
Antimicrobial agents used	6/20 (30%)
<i>Bleeding and coagulation</i>	
Bleeding from CVC insertion site	10/20 (50%)
Bleeding from mucosal area	3/20 (15%)
Prolonged BT (BT > 10 min)	0/20 (0%)
Prolonged CT (CT > 15 min)	0/20 (0%)
Prolonged PT (PT > 14 sec) [¶]	6/20 (30%) [15-19 sec]

Prolonged aPTT (aPTT > 40 sec) [¶]	3/20 (15%) [51-240 sec]
<i>Other complications</i>	
Saline responsive hypotension	10/20 (50%)
Anaemia (Hb < 8 gm/L)	2/20 (10%)
Thrombocytopenia (PC < 1.5 lac/ μ L) [¶]	6/20 (30%) [0.79-1.3 lac/ μ L]
Jaundice (serum bilirubin > 1.2 mg/dL)	0/20 (0%)
Renal impairment (serum creatinin > 1.2 mg/dL)	0/20 (0%)
Hyponatraemia (serum Na ⁺ < 135 mEq/L)	1/20 (5%) [126 mEq/L]
Hypokalaemia (serum K ⁺ < 3.5 mEq/L) [¶]	3/20 (15%) [2.6-3.2 mEq/L]
Hypoalbuminemia (serum albumin > 35 gm/L) [¶]	4/20 (20%) [26-32 gm/L]
Hypocalcaemia (serum Ca ⁺ < 2.2 mmol/L) [¶]	3/20 (15%) [1.89-1.98 mmol/L]
Hypomagnesaemia (serum Mg ⁺ < 75 mEq/L) [¶]	1/20 (5%) [73 mEq/L]
Hypersensitivity/transfusion reaction to FFP	4/20 (20%)

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692 ¶ Median (range); § rate per 1000 device days; CLABSI: central line-associated bloodstream

693 infection; VAP: ventilator-associated pneumonia; CAUTI: catheter-associated urinary tract

694 infection; CVC: central venous catheter; BT: bleeding time, CT: clotting time; PT: prothrombin

695 time; APTT: activated partial thromboplastin time; FFP: fresh frozen plasma.

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697 Table 3: Neurological outcomes of the 20 patients with GBS after SVPE
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Clinical outcome	1 month	2 months	3 months	6 months
Cranial nerve involvement	7/20 (35%)	6/20 (30%)	4/20 (20%)	2/20 (10%)
Autonomic involvement	3/20 (15%)	3/20 (15%)	0/20 (0%)	0/20 (0%)
Sensory dysfunction	1/20 (5%)	1/20 (5%)	1/20 (5%)	1/20 (5%)
GBS disability score [¶]	0 = 0	0 = 1	0 = 1	0 = 2
	1 = 3	1 = 6	1 = 7	1 = 7
	2 = 9	2 = 6	2 = 6	2 = 5
	3 = 2	3 = 1	3 = 1	3 = 3
	4 = 3	4 = 5	4 = 5	4 = 3
	5 = 3	5 = 1	5 = 0	5 = 0
MRC sum score [†] *	47 (0-60)	49 (0-60)	53 (6-60)	58 (22-60)
ONLS [‡] *	4 (1-12)	3 (0-12)	3 (0-12)	2 (0-10)
R-ODS [§] *	26 (0-41)	33 (0-45)	37 (0-45)	38 (0-46)

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700 * Median (range); ¶ GBS disability score (0 - 6) = 0: healthy state, 1: minor symptoms and

701 capable of running, 2: able to walk 10 meters or more without assistance but unable to run, 3:

702 able to walk 10 meters across an open space with help, 4: bedridden or chair-bound, 5: requiring

703 assisted ventilation for at least part of the day, 6: dead; † MRC sum score: Medical Research

704 Council sum score; ‡ ONLS: Overall Neuropathy Limitation Scale²²; § R-ODS: Rash-built

705 Overall Disability Score²³

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3 716 **Figure 1:** Feasibility of SVPE and associated complications for the 20 individual patients with
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5 717 GBS.

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9 719 SVPE: small volume plasma exchange, HAI: hospital acquired infection, V: ventilator-associated
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11 720 pneumonia, B: central line-associated blood stream infection, U: catheter-associated urinary tract
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13 721 infection, ^A measured in litres, ●: spell of hypotension (systolic BP < 90 mm Hg), ◊: CVC
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15 722 insertion site bleeding, ▲: hypersensitivity to fresh frozen plasma, shaded squares: pyrexia due to
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17 723 bacterial infection, dotted squares: pyrexia due to suspected viral infection, M: onset of mechanical
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19 724 ventilation, C: urinary catheterization.

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27 727 **Figure 2:** Hospital-acquired infections and use of antibiotics in the 20 patients with GBS receiving
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29 728 SVPE compared to the 24 hospital control patients without GBS treated in an ICU with a CVC who
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31 729 did not receive SVPE.

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34 731 ■ SVPE ($n = 20$): twenty patients with GBS aged ≥ 18 -years-old who were bedbound (GBS
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36 732 disability score ≥ 4) received small volume plasma exchange (SVPE) within 2 weeks of the onset
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38 733 of weakness. □ Non-SVPE ($n=20$): twenty-four patients aged ≥ 18 -years-old with a diagnosis
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40 734 other than GBS who required a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU
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42 735 and HDU units in the same period as the patients with GBS received SVPE; * $p < 0.0001$.

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50 738 **Figure 3:** Kaplan-Meier estimate (with 95% confidence limits) of the cumulative incidence of
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52 739 restoration of independent walking ability in patients with GBS treated with SVPE.

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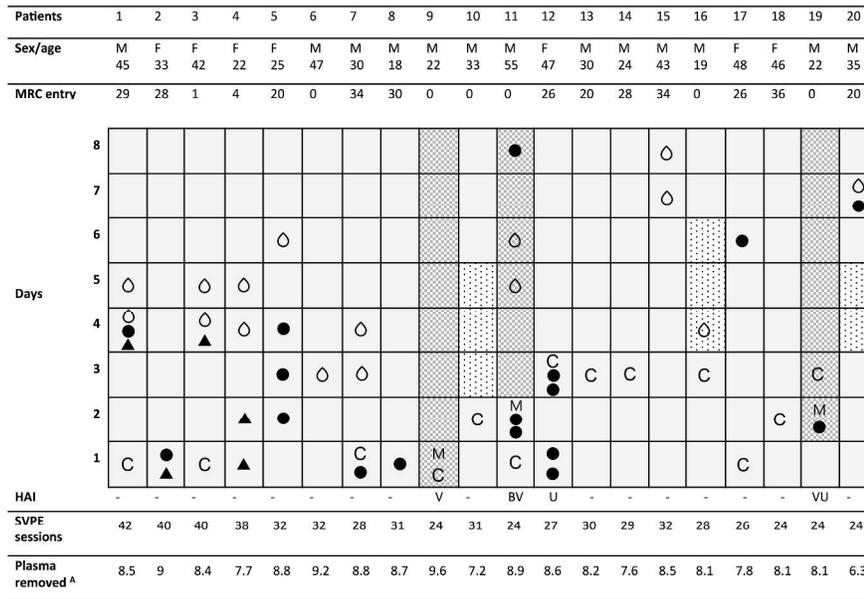


Figure 1: Feasibility of SVPE and associated complications for the 20 individual patients with GBS. SVPE: small volume plasma exchange, HAI: hospital acquired infection, V: ventilator-associated pneumonia, B: central line-associated blood stream infection, U: catheter-associated urinary tract infection, A measured in litres, black dot: spell of hypotension (systolic BP < 90 mm Hg), empty drop: CVC insertion site bleeding, black triangle: hypersensitivity to fresh frozen plasma, shaded squares: pyrexia due to bacterial infection, dotted squares: pyrexia due to suspected viral infection, M: onset of mechanical ventilation, C: urinary catheterization.

only

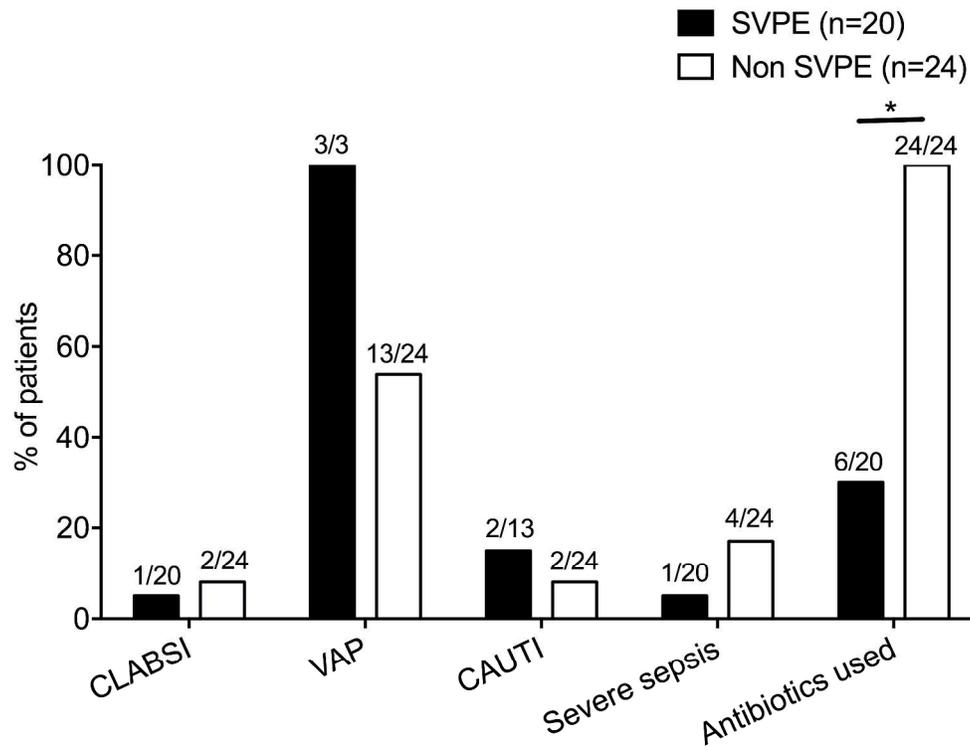


Figure 2: Hospital-acquired infections and use of antibiotics in the 20 patients with GBS receiving SVPE compared to the 24 hospital control patients without GBS treated in an ICU with a CVC who did not receive SVPE.

■ SVPE (n = 20): twenty patients with GBS aged ≥ 18 -years-old who were bedbound (GBS disability score ≥ 4) received small volume plasma exchange (SVPE) within 2 weeks of the onset of weakness. □ Non-SVPE (n=20): twenty-four patients aged ≥ 18 -years-old with a diagnosis other than GBS who required a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period as the patients with GBS received SVPE; * $p < 0.0001$.

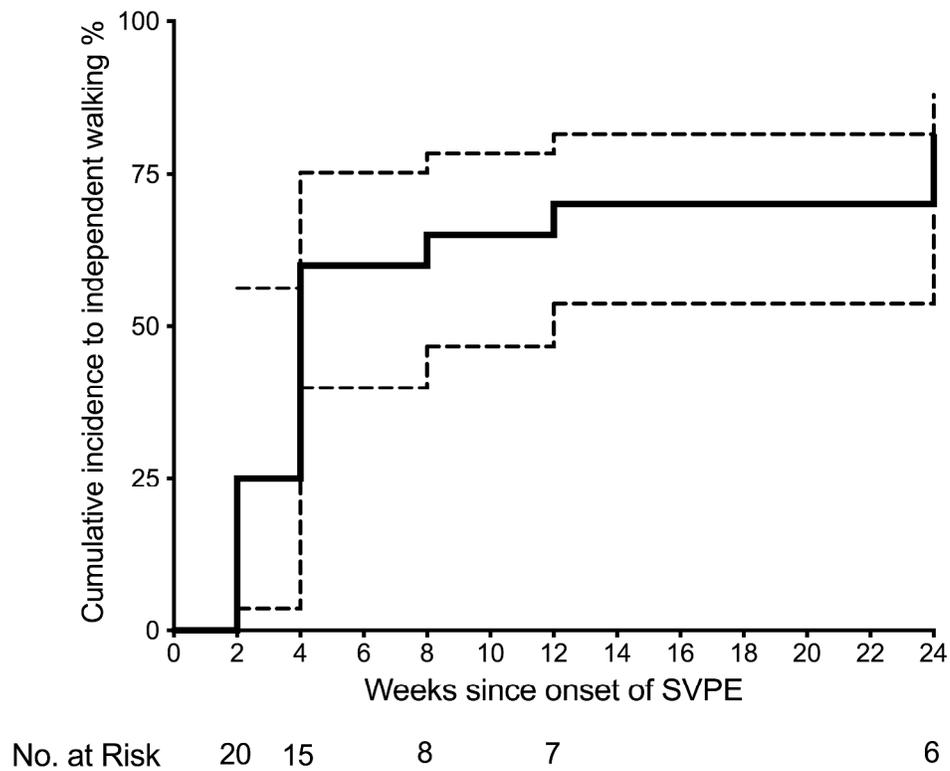
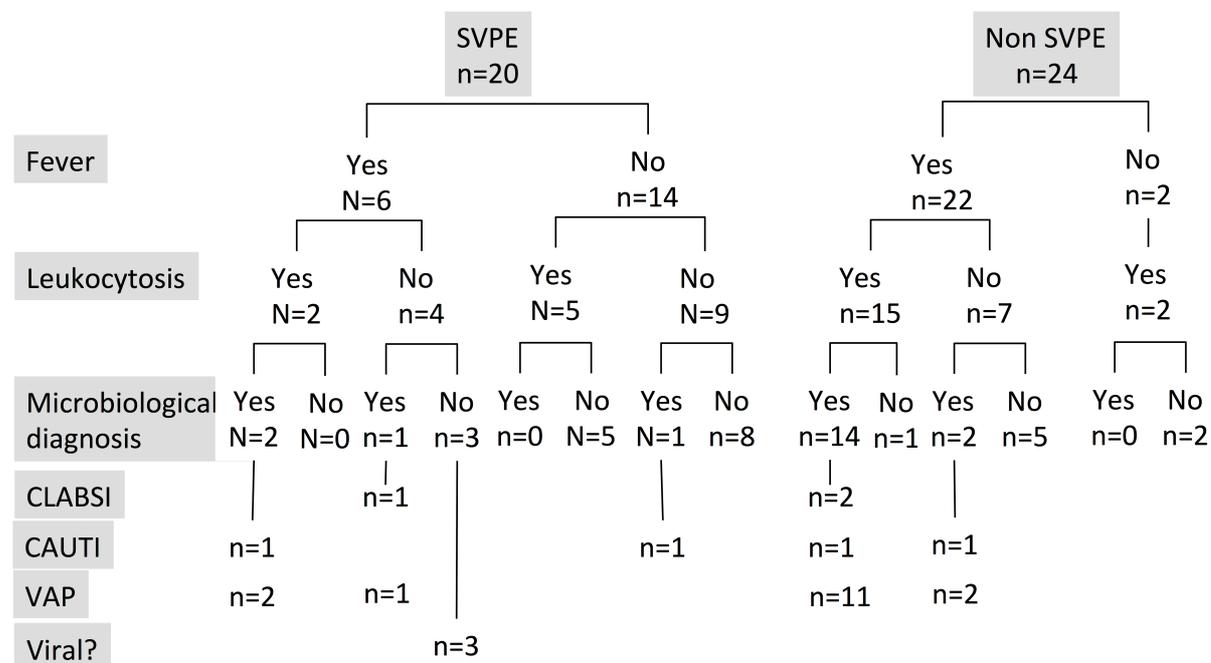


Figure 3: Kaplan-Meier estimate (with 95% confidence limits) of the cumulative incidence of restoration of independent walking ability in patients with GBS treated with SVPE.

Supplementary Figure: Hospital-acquired infections in the 20 patients with GBS treated with SVPE and the 24-hospital control patients without GBS.



SVPE: small volume plasma exchange, CLABSI: central line-associated blood stream infection, CAUTI: catheter-associated urinary tract infection, VAP: ventilator-associated pneumonia.

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2017 CONSORT checklist of information to include when reporting a randomized trial assessing nonpharmacologic treatments (NPTs)*.
Modifications of the extension appear in italics and blue.

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
Title and abstract					
	1a	Identification as a randomized trial in the title	NA (Non-randomized)		
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3, 4, 5	Refer to CONSORT extension for abstracts for NPT trials	3, 4, 5
Introduction					
Background and objectives	2a	Scientific background and explanation of rationale	6		
	2b	Specific objectives or hypotheses	6, 7		
Methods					
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7	When applicable, how care providers were allocated to each trial group	NA
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	No changes to methods after trial commencement		
Participants	4a	Eligibility criteria for participants	7, 8	When applicable, eligibility criteria for centers and for care providers	NA
	4b	Settings and locations where the data were collected	7		
Interventions†	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7, 8	Precise details of both the experimental treatment and comparator	7, 8
	5a			Description of the different components of the interventions and, when applicable, description of the procedure for tailoring the interventions to individual participants.	9
	5b			Details of whether and how the interventions were standardized.	8, 9

Cite as: Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40-7.

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
	5c.			Details of whether and how adherence of care providers to the protocol was assessed or enhanced	8, 9
	5d			Details of whether and how adherence of participants to interventions was assessed or enhanced	NA
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9		
	6b	Any changes to trial outcomes after the trial commenced, with reasons	No changes to trial outcomes after the trial commenced		
Sample size	7a	How sample size was determined	9	When applicable, details of whether and how the clustering by care providers or centers was addressed	NA
	7b	When applicable, explanation of any interim analyses and stopping guidelines	10		
Randomization:					
- Sequence generation	8a	Method used to generate the random allocation sequence	NA (Non-randomized)		
	8b	Type of randomization; details of any restriction (such as blocking and block size)	NA (Non-randomized)		
- Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	NA (Non-randomized)		
- Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	NA (Non-randomized)		
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Blinding was not possible	If done, who was blinded after assignment to interventions (e.g., participants, care providers, those administering co-interventions, those assessing outcomes) and how	Blinding was not possible

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Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
	11b	If relevant, description of the similarity of interventions	7, 8		
	11c			If blinding was not possible, description of any attempts to limit bias	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10	When applicable, details of whether and how the clustering by care providers or centers was addressed	NA
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA		
Results					
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	11	The number of care providers or centers performing the intervention in each group and the number of patients treated by each care provider or in each center	Single center study
	13b	For each group, losses and exclusions after randomization, together with reasons	No losses and exclusions after inclusion		
	13c			For each group, the delay between randomization and the initiation of the intervention	11
	new			Details of the experimental treatment and comparator as they were implemented	11-16
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7		
	14b	Why the trial ended or was stopped	NA (Trial completed)		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1	When applicable, a description of care providers (case volume, qualification, expertise, etc.) and centers (volume) in each group.	NA
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11-12		

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Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12-16		
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	15		
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12-15		
Discussion					
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	20-21	In addition, take into account the choice of the comparator, lack of or partial blinding, and unequal expertise of care providers or centers in each group	NA
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	16-20	Generalizability (external validity) of the trial findings according to the intervention, comparators, patients, and care providers and centers involved in the trial	16-20
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16-20		
Other information					
Registration	23	Registration number and name of trial registry	4		
Protocol	24	Where the full trial protocol can be accessed, if available	Manuscript reference no: 17		
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	22		

*Additions or modifications to the 2010 CONSORT checklist. CONSORT = Consolidated Standards of Reporting Trials

†The items 5, 5a, 5b, 5c, 5d are consistent with the Template for Intervention Description and Replication (TIDieR) checklist

Cite as: Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. *Annals of Internal Medicine*. 2017 Jul 4;167(1):40-7.

Table: Required documents of the safety and feasibility study of the small volume plasma exchange (SVPE) for Guillain-Barré syndrome patients for the World Health Organization Trial Registration Data Set

	Item/Label	Description
1	Primary Registry and Trial Identifying Number	Clinicaltrials.gov NCT02780570
2	Date of Registration in Primary Registry	May 23, 2016
3	Secondary Identifying Numbers	International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) Protocol Number: PR-15086, Version no. 3, Date: 09/12/2015
4	Source(s) of Monetary or Material Support	GBS/CIDP Foundation International Fondation Mérieux: (Small Grants Program 2015)
5	Primary Sponsor	GBS/CIDP Foundation International
6	Secondary Sponsor(s)	Fondation Mérieux: (Small Grants Program 2014)
7	Contact for public queries	MD. BADRUL ISLAM Email: bislamdmch@gmail.com Telephone no: +880 1712 89 0172 Postal address: Dr. Badrul Islam

		Research trainee and PhD Fellow Laboratory Sciences and Services Division (LSSD) Icddr,b Dhaka, Bangladesh
8	Contact for scientific queries	MD. BADRUL ISLAM Principal Investigator (PI) Email: bislamdmch@gmail.com Telephone no: +880 1712 89 0172 Postal address: Dr. Badrul Islam Research trainee and PhD Fellow Laboratory Sciences and Services Division (LSSD) Icddr,b Dhaka, Bangladesh
9	Public title	Small volume plasma exchange for Guillain-Barré syndrome
10	Scientific title	Small volume plasma exchange for Guillain-Barré syndrome in low-income countries: a safety and feasibility study
11	Countries of Recruitment	Bangladesh
12	Health condition(s) or problem(s) studied	Guillain-Barré syndrome (GBS)
13	Interventions	<u>Small Volume Plasma Exchange (SVPE)</u> A loading dose of low-molecular weight heparin (1.5 mg/kg) will be given subcutaneously at least two hours

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3 before initiation of SVPE; the same dose will be
4 administered once daily or divided into two equal doses
5 daily for eight days or until SVPE is completed. Whole
6 blood (7 mL/kg body weight) will be drawn from the
7 central venous catheter into the blood transfusion bag
8 in each session. The blood bag will be hung beside the
9 patient for 2.5 h on a saline stand and left
10 uninterrupted to allow plasma and blood cells to
11 separate. The blood cells will be infused back into the
12 patient and plasma will be discarded and replaced with
13 fresh frozen plasma and colloid solution alternately (in
14 equal volumes) via the closed-circuit SVPE kit illustrated
15 in. In case of excessive clotting (bleeding time reduction
16 of > 50% of baseline for that patient), aspirin (600 mg)
17 will be administered orally at least two hours before
18 the next SVPE session and continued thereafter at 150
19 mg orally/day until SVPE is completed. One blood bag
20 will be used each day, with a total of six sessions/day. A
21 total of 48 sessions will be performed over eight days,
22 removing approximately 8000 mL plasma in total.
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39 Central venous catheterized patients without GBS

40 To compare the safety of SVPE in patients with GBS in
41 the context of the background risk of central line-
42 associated blood stream infection (CLABSI) at the study
43 intensive care (ICU) and high-dependency care (HDU)
44 units, the incidence of CLABSI will be assessed in a
45 control group of adult patients with a diagnosis other
46 than GBS admitted to the same ICU and HDU units in
47 the same period of time the patients with GBS will be
48 enrolled for SVPE. We will assess the rate of CLABSI in
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		<p>patients aged ≥ 18-years-old requiring a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units.</p>
14	<p>Key Inclusion and Exclusion Criteria</p>	<p><u><i>Inclusion criteria for SVPE in GBS patients</i></u></p> <ol style="list-style-type: none"> 1. Patients aged ≥ 18-years-old fulfilling the diagnostic criteria for GBS of the National Institute of Neurological and Communicative Disorders and Stroke (NINDS) 2. Unable to walk unaided for more than 10 meters (GBS disability score ≥ 3) 3. Presented within 2 weeks of the onset of weakness 4. Unable to afford standard treatment with IVIg or PE. <p><u><i>Exclusion criteria for SVPE in GBS patients</i></u></p> <ol style="list-style-type: none"> 1. Patients with severe or terminal concomitant illness 2. Evidence of healthcare-associated infection on admission (except for aspiration pneumonia) 3. Previous history of severe allergic reaction to properly matched blood products and pregnant women will be excluded from the study. <p><u><i>Inclusion criteria for patients without GBS</i></u></p> <ol style="list-style-type: none"> 1. Patients aged ≥ 18-years-old 2. Requiring a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period of time the patients with GBS enrolled for SVPE. <p><u><i>Exclusion criteria for patients without GBS</i></u></p>

		<ol style="list-style-type: none"> 1. Patients with healthcare-associated infection present on admission (except aspiration pneumonia) 2. Pregnant women
15	Study type	<p><u>Type of the study:</u> Interventional</p> <p><u>Method of allocation:</u> Non-randomized</p> <p><u>Masking:</u> Non-masked</p> <p><u>Assignment:</u> Parallel arm</p> <ul style="list-style-type: none"> • SVPE in patients with GBS • Rate of CLABSI in patients without GBS <p><u>Purpose:</u> Safety and feasibility of SVPE</p>
16	Date of first enrolment	February 20, 2016
17	Target sample size	<p>SVPE in patients with GBS = 20</p> <p>Rate of CLABSI in patients without GBS = ≥ 20</p>
18	Recruitment status	<p>Completed:</p> <ul style="list-style-type: none"> • Twenty cases of GBS have been successfully treated with SVPE and 24 control cases without GBS have been recruited.
19	Primary Outcome(s)	<p><u>Primary outcome of safety:</u></p> <ol style="list-style-type: none"> 1. Number of patients with GBS treated with SVPE developing severe sepsis or septic shock due to central line associated blood stream infection (CLABSI) as per standard guideline (Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central line-associated Bloodstream Infection); CDC Device-associated Module, BSI. January 2017) 2. Occurrence of venous thrombosis in the limb

		<p>where the CVC is placed. Venous thrombosis will be assessed according to Wells criteria (Philip S. Wells et al. Evaluation of d -Dimer in the Diagnosis of Suspected Deep-Vein Thrombosis; N Engl J Med 2003;349:1227-35)</p> <p><u>Primary outcome of feasibility:</u></p> <ol style="list-style-type: none"> 1. Ability to remove at least eight litres of plasma by SVPE over eight days.
20	Secondary Outcome(s)	<p><u>Secondary outcome of safety:</u></p> <ol style="list-style-type: none"> 2. Relative risk of CLABSI due to SVPE compared to CLABSI in control patients without GBS treated using a CVC 3. Hemodynamic instability during the SVPE procedure (variations in systolic blood pressure greater than 30 mmHg or sudden bradycardia involving a reduction in heart rate by more than 20 beats per min within 30 min of starting SVPE or an increase in heart rate above 120 beats per min) 4. Development of anaemia (Hb <7 gm/dL) or serious haemorrhage requiring blood transfusion. <p><u>Secondary outcome of feasibility:</u></p> <ol style="list-style-type: none"> 1. Rate of CVC occlusion during the SVPE procedure 2. The healthcare personnel's acceptability and

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		<p>satisfaction with the SVPE procedure and any unanticipated events compromising the SVPE procedure as assessed using a standard questionnaire.</p> <p>3. Neurological outcome will be assessed in terms of improvement in GBS disability score and MRC sum score at discharge and up to 4 weeks after entry.</p>
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For peer review only